REP0114

PROTOCOL No. REP0114 (Final Version 9.0 – 25 November 2019)
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A randomized, double-blind, placebo-controlled phase 2 study of paclitaxel in combination with reparixin compared to paclitaxel alone as front-line therapy for Metastatic Triple-Negative Breast Cancer (FRIDA)

Study Phase: II
Investigational Medicinal Product: Reparixin oral tablets
IND number: 112502
EudraCT number: 2014-004796-23

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APPROVAL OF THE PROTOCOL

Approved and Signed by		**Date**
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Susan McCanna, BSc	_____ Dompé Farmaceutici s.p.a. – Clinical Development Manager	___/___/____

I have read and agree to the protocol REP0114, entitled '**A randomized, double-blind, placebo-controlled phase 2 study of paclitaxel in combination with reparixin compared to paclitaxel alone as front-line therapy for Metastatic Triple-Negative Breast Cancer**'. I am aware of my responsibilities under the guidelines of GCP, local regulations (as applicable), the declaration of Helsinki, and the study protocol. I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the study.

Clinical Site Name:	
Site Number:	
Site Principal Investigator:	
Signature/Date:	

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1 GENERAL INFORMATION

TITLE	A randomized, double-blind, placebo-controlled phase 2 study of paclitaxel in combination with reparixin compared to paclitaxel alone as front-line therapy for Metastatic Triple-Negative Breast Cancer (FRIDA)
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1.1 Protocol Summary

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Study Number: REP0114
Title of Study: A randomized, double-blind, placebo-controlled Phase 2 Study of paclitaxel in combination with reparixin compared to paclitaxel alone as front-line therapy for Metastatic Triple-Negative Breast Cancer (FRIDA)
Investigational Medicinal Product: Reparixin oral tablets
Study Sites: Approximately 60 sites located in the USA and EU
Phase of Development: II
Background information Cancer Stem Cells (CSCs) have the ability to self-renew and generate the full range of cells that make up a bulk tumor. CSC have been identified in several human haematological and non-haematological tumors. In breast cancer, CSC were originally identified as cells expressing the CD24-CD44+ phenotype (Al-Hajj, et al., 2003). Later, CSC in breast and other human cancers were found to express the enzyme aldehyde dehydrogenase (ALDH+). Gene expression profiling of the ALDH+ populations in breast cancer (BC) revealed selective expression of CXCR1, a receptor for the cytokine CXCL8 (formerly, IL-8). CXCR1 expression was limited to a subpopulation of ALDH+ cells. *In vitro*, the addition of recombinant CXCL8 increased the CSC population as well as its propensity for invasion (Charafe-Jauffret, et al., 2009). Using CXCR1-blocking antibodies or reparixin (a small molecular weight allosteric inhibitor of CXCR1), it was demonstrated that CXCR1 blockade selectively decreased the breast CSC population *in vitro* and in NOD/SCID xenograft models. Furthermore, administration of reparixin in combination with chemotherapy to tumor bearing NOD/SCID mice reduced tumor burden and the proportion of both ALDH+ and CD24-CD44+ BC CSCs. Finally, administration of reparixin single agent reduced development of systemic breast cancer metastasis in NOD/SCID mice. These studies provide experimental support to strategies aimed at interfering with the CXCL8/CXCR1 axis, which is activated by conventional chemotherapy. CXCR1 inhibition may be able to target BC CSCs and increase the efficacy of current therapies which address the proliferating, non-CSC component of the tumor. Clinical investigation of reparixin as a BC CSC targeting agent was started in metastatic BC. In keeping with the animal model, three dose levels of reparixin (400 mg, 800 mg and 1200 mg three times daily) were administered in combination with weekly paclitaxel 80 mg/m^2, in a phase Ib clinical trial, open to patients with non-HER2 amplified metastatic BC. The study provided evidence that the combination is safe and well tolerated across the three dose levels explored, with a MTD not having been formally reached, and produces a sizeable response rate with some long term responders. Reparixin 1200 mg t.i.d. was chosen as recommended phase II dose. Among non-HER2 amplified BC, Triple Negative BC (TNBC) is a subtype where <1% of the cells express estrogen or progesterone receptors (Hammond, et al., 2010). As a consequence, TNBC is amenable neither to hormonal nor to HER2-targeted therapies, with the only treatments available consisting of surgery, radiotherapy and chemotherapy. Metastatic TNBC carries a dismal prognosis, with median overall survival not exceeding 13 months (Kassam, et al., 2009). Similar to other BC types, treatment of metastatic TNBC is based upon sequential monotherapies in all patients, except those with a rapidly progressing or highly symptomatic

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disease. Most patients with metastatic TNBC relapsed following a (neo)adjuvant chemotherapy regimen which most often contains a taxane (i.e., paclitaxel or docetaxel). Patients who relapsed following a taxane-containing (neo)adjuvant regimen can be re-challenged with a taxane as long as a sizeable Disease-free/Progression-free survival has been recorded.
Among BC subtypes, TNBC is the one where CSCs are most represented. Considering its dismal prognosis, its sensitivity to single agent paclitaxel even in the re-challenge setting, and the safety and activity data of the combination reparixin + weekly paclitaxel as assessed in the phase Ib study, this randomized phase 2 clinical trial aims at formally evaluating activity and safety of the combination in comparison with single agent weekly paclitaxel in patients with metastatic TNBC.

Study Objectives:

Primary Objective

- The primary objective of the study is to evaluate Progression Free Survival (PFS) (defined as the number of days between the date of randomization and the date of clinical disease progression (PD) according to RECIST criteria version 1.1, as assessed by Independent Radiology Review, or death for any cause, whichever occurs first) in patients with metastatic TNBC treated with the combination of paclitaxel and orally administered reparixin compared to paclitaxel alone.

Secondary Objectives

- To determine Overall Survival (**OS**)
- To evaluate Objective Response Rates (**ORR**)
- To determine median PFS (mPFS)
- To assess the safety of the combination treatment

Exploratory Objectives

- To determine Median Time To new Metastasis (**TTM**) (new lesions at existing or new sites)
- To determine Proportion of patients progressing with new metastatic lesions
- To compare the incidence and severity of peripheral neuropathy between the two treatment groups
- Evaluation of CSCs in metastatic tissue

Study Design and Methodology:

Randomized (1:1), double-blind, placebo-controlled, multicentre phase II clinical trial.

Treatment Groups:

Group 1: paclitaxel 80 mg/m^2 i.v. (Days 1, 8, and 15) + reparixin oral tablets 1200 mg t.i.d. continuing from D 1 to Day 21 of 28-day cycle

Group 2: paclitaxel 80 mg/m^2 i.v. (Days 1, 8, and 15) + placebo oral tablets 1200 mg t.i.d. continuing from D 1 to Day 21 of 28-day cycle

Number of Patients:

The trial is designed to provide 80% statistical power to detect an improvement in PFS from 5 months with paclitaxel monotherapy in patients with metastatic TNBC (Awada, et al., 2014;

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Finn, et al., 2009, Harris, et al., 2006; Miller et al, 2007) to 8 months with the addition of Reparixin, corresponding to a hazard ratio 0.625, when using a logrank statistic having (one-sided) 0.025 false positive error rate. This requires 142 PFS events and the approximate sample size will be 156 randomized patients (78 patients per group). Due to extreme enrollment difficulties during the first 6 months of 2018, enrollment to the study was terminated early (30 July 2018) and the final sample size is equal to 123 randomized patients. No formal recalculation of sample size/required PFS events could be made under these circumstances and although the above assumptions remain, the true statistical power and hazard ratio will be known after database lock and will be presented in the CSR.
Duration of Study Drug Treatment: 28-day cycles of combination therapy reparixin oral tablets + paclitaxel i.v. weekly (group 1) or placebo oral tablets + paclitaxel i.v. weekly (group 2) three weeks on and one week off until disease progression by RECIST version 1.1, withdrawal of consent, or unacceptable toxicity, whichever occurs first.
Test Product; Dose and Mode of Administration: Reparixin or placebo 600 mg oral tablets Reparixin or placebo will be administered at the dose of 1200 mg three times daily (2 x 600 mg tablets every six to ten hours) for 21 consecutive days (days 1-21) during each 28 day cycle. Paclitaxel will be administered i.v. 80 mg/m^2 on Days 1, 8 and 15 of a 28-day cycle.

Inclusion Criteria:

To be checked at the pre-study visit within 14 days before study treatment:

- Female aged ≥ 18 years.
- Patients with pathologically documented metastatic triple negative breast cancer (TNBC), eligible for treatment with paclitaxel. **Paraffin-embedded tissue must be available from metastatic sites, if reasonably accessible, or from the primary tumor, to confirm the diagnosis of TNBC and for correlative studies (only on metastatic tissue).** Fifteen slides can be obtained if the full block is not available to be sent or released.
  TNBC will be defined as breast cancer with <1% ER+ and <1% PgR+ cells, and HER2 immunohistochemistry score of 0 or 1+ and/or in situ hybridization (ISH) with HER2 gene copy number <4 or a ratio of less than 2 between HER2 gene copy number and centromere of chromosome 17. Patients whose metastatic disease is TNBC are eligible even when their primary tumor expressed hormone receptors and/or HER2.
- Patients must be newly diagnosed metastatic or must have relapsed following a prior (neo)adjuvant chemotherapy regimen. If a taxane (i.e., paclitaxel or docetaxel) was administered as part of the (neo)adjuvant regimen, PD must have occurred > 12 months from the end of previous (neo)adjuvant treatment. For non-taxane (neo)adjuvant regimen, PD must have occurred > 6 months from the end of previous (neo)adjuvant treatment. .
- Patients with at least one baseline measurable lesion according to RECIST criteria version 1.1.
- Zubrod (Eastern Co-operative Oncology Group [ECOG]) Performance Status (PS) of 0-1.
- Life expectancy of at least three months.
- Patients must be able to swallow and retain oral medication (intact tablet).
- Able to undergo all screening assessments outlined in protocol.
- Adequate organ function (defined by the following parameters):
  a) Serum creatinine < 140 µmol/L (< 1.6 mg/dL) or creatinine clearance > 60 mL/min.
  b) Serum hemoglobin ≥ 9 g/dL; absolute neutrophil count ≥ 1.5 x 10^9/L; platelets ≥ 100 x 10^9/L.
  c) Serum bilirubin ≤ 1.5 x upper normal limit (UNL), except patients with Gilbert's syndrome.
  d) Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≤ 2.5 x UNL but ≤ 5.0 x UNL in case of liver metastases; alkaline phosphatase (ALP) ≤ UNL but *i*) ≤ 2.5 x UNL in case of liver metastases and *ii*) ≤5 x UNL in case of bone metastases; albumin ≥ 2.5 g/dl .
- No history or evidence by CT scan or MRI, of brain metastases or leptomeningeal disease.
- No known hepatitis B virus (not due to immunization), hepatitis C virus, human immunodeficiency virus-I and -II positive status.
- No history or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or

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Medical Monitor, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

- Dated and signed IEC/IRB-approved informed consent

Exclusion Criteria:

- Prior therapy for metastatic TNBC (chemotherapy, hormone therapy or biological therapy). Patients may receive bisphosphonates and other therapies to treat bone metastases, however if used, bone lesions will not be considered as measurable disease.
- Less than four weeks since last radiotherapy (excluding palliative radiotherapy).
- Pregnancy or lactation or unwillingness to use adequate method of birth control
- Neurological or psychiatric disorders which may influence understanding of study and informed consent procedures.
- Active or uncontrolled infection.
- Malabsorption syndrome, disease significantly affecting gastrointestinal function.
- G>1 pre-existing peripheral neuropathy.
- Any other invasive malignancy from which the patient has been disease-free for less than 5 years with the exception of curatively treated basal or squamous cell skin cancer
- Hypersensitivity to:
  a) paclitaxel
  b) ibuprofen or to more than one non-steroidal anti-inflammatory drug.
  c) more than one medication belonging to the class of sulfonamides, such as sulfamethazine, sulfamethoxazole, sulfasalazine, nimesulide or celecoxib; hypersensitivity to sulphanilamide antibiotics alone (e.g. sulfamethoxazole) does not qualify for exclusion.

Criteria for Evaluation:

Efficacy: Disease status (up to progression of disease [PD]) will be measured by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 at screening and every eight weeks until study end. Evaluation of disease status will be performed at the participating clinical site. An independent radiological review of images for disease response and PFS measurement will also be performed.

Safety: Recording of adverse events (AEs), clinical examinations, hematology parameters, clinical chemistry parameters, urinalysis, vital signs, chest X-ray, physical examination, Zubrod PS will be performed according to the study flow chart included in the protocol.
An independent Data Monitoring Committee will assess safety periodically.

Correlative studies:

1) Paraffin-embedded metastatic tumor tissue

The following analyses will be performed on sections of paraffin embedded tissue:

- Evaluation of CD24-CD44+ CSC
- Evaluation of ALDH+ CSC

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Statistical Methods:

For the primary endpoint, PFS as measured from time of randomization to time to disease progression or death, whichever occurs first, will be compared between treatment arms using stratified log-rank test..

Kaplan-Meier curves will be generated to estimate themedian PFS in the intent-to-treat population (all randomly assigned patients). Kaplan-Meier curves will also be produced for OS outcomes. In a supportive analysis, a Cox regression analysis will be performed. Patients will be randomized to the two treatment groups with a 1:1 ratio. Randomization will be stratified between two subpopulations, newly diagnosed metastatic patients and patients that have relapsed following a prior (neo)adjuvant chemotherapy regimen.

The disease response (disease status up to PD) at pre-study (baseline) and every eight weeks until the end of the study based on the RECIST version 1.1 criteria will be summarized by counts and percents.

Safety and tolerability analysis will be applied on the safety population (all patients having taken at least one dose of the study treatment). AEs, physical examination, vital signs, concomitant medications and laboratory data will be considered for the safety analyses. Descriptive statistics will be provided for these variables.

Study Procedures:

Patients will be assessed for eligibility and will have the following procedures done during the 14 days prior to start of treatment (with the exception of x-rays, scans and tumor tissue which will be done during the 28 days prior to start of treatment): medical history, physical exam, labs, x-rays and/or CT scans, including a CT scan or MRI of the brain. A sample of tumor tissue will be collected for analysis.

Laboratory tests performed within 14 days prior to screening period even if before ICF signed are acceptable.

During study participation and while the patient is receiving study treatment, the patient will continue to be followed with physical exams, a pregnancy test prior to each treatment cycle, review of concomitant medications and adverse events, labs, and scans (CT, MRI etc,). The patient will also complete a diary to record intake of study medication.

After completion of study treatment, the patient will be followed for 30 days to assess safety, and then followed until death, to assess disease status, new treatments, and survival status or until 30 September 2019 **(1 year after last enrolled subject off treatment)**, whichever occurs first.

Please refer to section 1.2, Study Flow Chart for full details.

1.2 Study Flow Chart

Procedure	Pre-Study[1]	Treatment Cycles[14]				OTV[15]	Long term Follow up[16]
		D1	D8	D15	D21		
Eligibility criteria	X						
Demographic data/tumor characteristics	X						
Tumor history surgery, radiotherapy, systemic therapies	X						
Medical history	X						
Disease status	X[2,3]	Every 8 weeks[4]				X[3]	
Physical examination	X	X[5]				X	
Vital signs (BP, pulse)[6]		X				X	
ECG	X						
Chest X-ray (if not already performed to follow tumor. Thoracic CT scan may substitute chest X-ray)	X					X	
Zubrod PS	X					X	
Urinalysis	X[7]	As clinically indicated				X[7]	
Hematology	X[8]	X[8]	X[8]	X[8]		X[8]	
Clinical chemistry	X[9]	X[9]	As clinically indicated			X[9]	

D1 = Day 1 etc, OTV = off-treatment visit

1 All pre-study examinations should be performed within 14 days (± 1 day window) of beginning study treatment unless otherwise specified. Informed consent should be signed before any study specific procedures are performed (with the exception of routine lab tests).

2 Pre-study disease evaluation should be obtained within 28 days of study treatment initiation.

3 Disease evaluations and a brain CT or MRI will be performed at pre-study. The scans (with exception of brain scans) will be repeated every eight weeks until documented PD. A brain scan will be repeated if patient presents with symptoms of brain metastases or PD of baseline lesions. At study end, a Best Overall Response Assessment (BOR) will be made: the disease assessments do not need to be repeated if done within four weeks prior to the off treatment visit. Copies of all scans (CT, MRI of chest abdomen, pelvis etc) will be submitted to the central radiology vendor for review at each time point.

4 For tumor assessment (i.e. scans) beginning at Week 8, a ± 3-day window will be allowed.

5 Physical exam, including weight will be performed at pre-study and Day 1 of each cycle beginning with cycle 2. Pretreatment signs and symptoms, height, and BSA will also be collected at the pre-study visit only.

6 Vital signs must be performed within 24 hours prior to the first study drug (reparixin/placebo) administration , and then on Day 1 of subsequent cycles.

7 PH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocytes and urobilinogen (by dipstick or in lab) at pre-study, as clinically indicated, and at off-treatment visit. Laboratory tests performed within 14 days screening period even if before ICF signed are acceptable.

8 Hematology tests: hemoglobin, WBC and differential WBC, platelets at pre-study and on Days 1, 8 and 15 of each cycle and at the off-treatment visit. Routine laboratory tests performed within 14 days screening period even if before ICF signed are acceptable

9 Clinical chemistry tests: sodium, potassium, calcium, serum creatinine, total protein, albumin, AST, ALT, ALP, urea, total bilirubin at pre-study, on Day 1 of treatment cycles and as clinically indicated and at the off treatment visit. Laboratory tests performed within 14 days screening period even if before ICF signed are acceptable.

Procedure	Pre-Study[1]	Treatment Cycles[14]				OTV[15]	Long term Follow up[16]
		D1	D8	D15	D21		
Urine or serum pregnancy test	X[10]	X[10]				X[10]	
Record concomitant treatments	X	Throughout study				X	
AE monitoring		Throughout study				X	
Peripheral neuropathy monitoring	X	Throughout study				X	
Reparixin/Placebo administration[11]		Continuously days 1 to 21					
Paclitaxel administration		X	X	X			
Dispense diary card[12]		X				X review only	
Tumor tissue (archival or new biopsy)[13]	X						
Date of progression and documentation of additional cancer therapy (if not off study due to PD) and Survival Status							X

10 Urine or serum pregnancy test required for women of childbearing potential only
11 Study drug (Reparixin/Placebo) administered orally every 6 to 10 hours t.i.d. for 21 consecutive days during each cycle with seven days off treatment between each cycle
12 Patients will be given a diary card to record information about date, time and dose taken. At each scheduled visit before the start of a new cycle of dose administration and at OTV, the diary should be reviewed with the patient for completeness.
13 Tumor tissue will be sampled within 28 days of study treatment initiation, to confirm recurrence of metastatic breast cancer, confirm TNBC, and to conduct the following correlative studies: evaluation of CD24-CD44+CSC, ALDH+CSC.
14 During Cycle 1, a ± 1-day window will be allowed for study visits. After Cycle 1, a ± 2-day window will be allowed for study visits.
15 Off treatment Visit to be performed 14 to 28 days following the last dose of study drug. Patients with ongoing treatment-related AEs still present in the 30 days after treatment discontinuation should continue to be followed until recovery or assessment of chronicity or as instructed by the medical monitor. Patients off treatment without documented PD should continue to have disease assessments every 8 weeks until PD or another anti-cancer therapy is initiated, whichever comes first.
16 Following PD, survival status will be collected every 3 months until death or until 30 September 2019 (1 year after last enrolled subject off treatment), whichever occurs first.

1.3 List of Abbreviations and Definition of Terms

ABC	ATP-binding cassette
ADR	Adverse drug reaction
AE	Adverse event
AKT	Serine-threonine protein kinase (also known as protein kinase B, PKB)
ALDH1+	Aldehyde dehydrogenase 1 positive
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase (serum glutamate pyruvate transaminase)
AST (SGOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC_{0-8}	Area under the plasma concentration-time curve from time zero to 8 hours post-dosing
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 hours post-dosing
AUC_{inf}	Area under the plasma concentration-time curve from time zero to infinity
AUC_{tau}	Area under the plasma concentration-time curve for a dosing interval
AUC_{tot}	Overall exposure
b.i.d.	bis in die (twice daily)
BOR	Best overall response
BP	Blood pressure
BSA	Body surface area
CBR	Clinical benefit rate
CFR	Code of Federal Regulations
CL/F	Oral clearance
C_{max}	Maximal concentration
CMH	Cochran-Mantel-Haeszel
C_0	Concentration at pre-dose
CPB	Cardiopulmonary bypass
CR	Complete remission/response
CRF	Case Report Form
CRO	Contract Research Organization
CSC	Cancer stem cell
C_{ss}	Concentration at steady-state
CT	Computed tomography
CTC	Circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
CXCL8; IL-8	Interleukin-8
CXCR	chemokine receptor
CXCR-1	Chemokine receptor 1
CXCR-2	Chemokine receptor 2
CYP2C19	Cytochrome P450 2C19
CYP2C9	Cytochrome P450 2C9
CYP3A4	Cytochrome P450 3A4
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
ECOG	Eastern Co-operative Oncology Group
EGFR	Epidermal growth factor receptor
EMT	Epithelial-mesenchymal transition
EOC	End of cycle
ER	Estrogen receptor
FAK	Focal adhesion kinase
FAS/FASL	Fas/Fas ligand
FDA	Food and Drug Administration
FISH	Fluorescence in Situ Hybridization
GCP	Good Clinical Practice
GI	Gastrointestinal
GM-CSF	Granulocyte macrophage colony stimulating factor
HED	Human equivalent dose

HER-2	Human epidermal growth factor receptor-2
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IL	Interleukin
IL-1β	Interleukin-1beta
IL-6	Interleukin-6
IMP	Investigational Medicinal Product
IRB	Independent Review Board
IRR	Independent Radiology Review
IRT	Interactive Response Technology
i.v.	Intravenous
K_{el}	Terminal elimination rate constant
kg	Kilogram
L	Litre
LD	Longest diameter
LFT	Liver function test
LPS	Lipopolysaccharide
max	Maximum
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minimum
mL	Milliliter
mm	Millimeter
m^2	Square meter
MTD	Maximum tolerated dose
n	Number of patients
NIMP	Non-investigational Medicinal Product
NOAEL	No Observed Adverse Effect Level
NOD/SCID	Non-obese diabetic/severe combined immunodeficiency disease
NOEL	No Observed Effect Level
PD	Progression of disease/disease progression
PDG/DGF	Primary Graft Dysfunction/Delayed Graft Function
PgR	Progesterone receptor
PK	Pharmacokinetic
PMN	Polymorphonuclear leukocytes
p.o.	Orally
PR	Partial remission/response
PS	Performance status
PTEN	Phosphatase and tensin homolog
Rac	Accumulation ratio
RECIST	Response Evaluation Criteria In Solid Tumors
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SOPs	Standard Operating Procedures
T1D	Type 1 diabetes
TEAE	Treatment-emergent adverse event
t.i.d.	ter in die (3 times daily)
TNBC	Triple Negative Breast Cancer
TNF-α	Tumor necrosis factor-alpha
t_{max}	Time to maximum plasma concentration
$t_{½}$	Terminal half-life, calculated as (ln 2)/λz
TTP	Median time to tumor progression in days
UNL	Upper normal limit
USA	United States of America

Vz	Apparent volume of distribution during the terminal phase
Vz/F	Apparent volume of distribution following oral administration
WBC	White blood cell

2 INTRODUCTION

2.1 Cancer Stem Cells

According to the cancer stem cell (CSC) model, tumors are initiated and maintained by a cellular subcomponent that displays stem cell properties. These properties include self-renewal, which drives tumorigenesis, and differentiation (albeit aberrant), which contributes to tumor cellular heterogeneity. The existence of CSCs has been described in a variety of haematologic and solid tumors including those of the breast, brain, colon, pancreas, lung, liver, and head and neck (Visvader, et al., 2008).

In addition to driving tumorigenesis, CSCs may contribute to tumor metastasis as well as to tumor recurrence after treatment (Reya, et al., 2001). Although currently available drugs can shrink metastatic tumors, these effects are usually transient and often do not appreciably extend the life of patients. One reason for the failure of these treatments is the acquisition of drug resistance by the cancer cells as they evolve; another non-mutually exclusive possibility is that existing therapies fail to kill CSCs. (Cojoc, et al., 2014) The ability to shrink a tumor mass mainly reflects an ability to kill bulk, non CSC tumor cells. This is because CSCs represent only a tiny percentage of the total tumor cells in a neoplastic lesion and the majority of the bulk tumor cells have limited proliferative potential. It seems that normal stem cells from various tissues tend to be more resistant to chemotherapeutics than mature cell types from the same tissues. The reasons for this are not clear, but may relate to high levels of expression of anti-apoptotic proteins or ATP-binding cassette (ABC) transporters such as the multidrug resistance gene. If the same were true of CSCs, then one would predict that these cells would be more resistant to chemotherapeutics than bulk tumor cells with limited proliferative potential. Even therapies that cause complete regression of tumors might spare enough CSCs to allow regrowth of the tumors. Thus, therapies that are more specifically directed against CSCs might result in much more durable responses and even cures of metastatic tumors (Reya, et al., 2001).

2.2 Reparixin Background

2.2.1 Drug Description and Mechanism of Action

Reparixin (DF1681Y, formerly repertaxin) is a specific inhibitor of CXC ligand 8 [CXCL8; formerly IL-8] biological activity, stemming from a program of drug design of molecules intended to modulate chemokine action (Reparixin Investigator's Brochure, 2014).

Reparixin is the first low molecular weight blocker of CXCL8 biological activity in clinical development. Relevant pre-clinical, toxicological and Phase I and II clinical data are summarized below. Please also refer to the Investigator's Brochure for more detailed information.

2.2.2 Pharmacological Profile

Reparixin (formerly repertaxin) is a novel, potent and specific inhibitor of the biological activity of the chemokine CXCL8 (Reparixin Investigator's Brochure, 2014).

Mechanism of action studies have shown that reparixin is a non-competitive allosteric inhibitor of the CXCL8 receptors CXCR1 and CXCR2. Interaction of repertaxin with CXCL8 receptors

inhibits the intracellular signal transduction events activated by binding of CXCL8 to CXCR1 and CXCR2. Chemical computational studies and alanine scanning mutagenesis have identified the interaction site between reparixin and CXCR1/2 in the transmembrane region of CXCR1 and CXCR2 (Bertini, et al., 2004 & Allegretti, et al., 2005).

A number of *in vitro* and in *vivo* assays on recognized breast cancer models have been conducted in support of the planned clinical development in Oncology. *In vitro* assays to assess the effect of reparixin on breast cancer cell growth showed that reparixin reduces metabolic capability and also reduces cell number. *In vitro* chemotaxis of rat polymorphonuclear leukocytes (PMN) induced by the rat counterparts of human CXCL8 was also inhibited by reparixin. In vivo modelling studies of advanced breast cancer with CXCR1 inhibition in the presence of conventional chemotherapeutics (docetaxel and paclitaxel) demonstrate that reparixin specifically targets and reduces the CSC population. Both docetaxel and paclitaxel target the differential tumor cells, the association of docetaxel or paclitaxel with reparixin is capable of dramatically reducing both the bulk of the tumor mass as well as resident CSC population (Reparixin Investigator's Brochure, 2014).

2.2.3 PHARMACOKINETICS AND PRODUCT METABOLISM

Pharmacokinetic (PK) studies by intravenous (i.v.) injection revealed that reparixin is very rapidly eliminated in rats and humans ($t_{1/2}$ 0.5-3 hours and 1.0-1.5 hours, respectively) whereas elimination is slower in dogs (12-28 hours). The PK of reparixin was linear in rats and in dogs but linearity was less evident in humans (Reparixin Investigator's Brochure, 2014).

Reparixin undergoes complete metabolism (oxidation + conjugation) in all the species tested. The *in vitro* human hepatic phase I metabolism of reparixin is catalyzed by CYP2C9 and to a lesser extent by CYP2C19. DF2243Y, DF2188Y, methanesulfonamide and ibuprofen are the metabolites detected in human plasma and urine, with DF2243Y being the major metabolite. Exposure to ibuprofen after administration of reparixin 2.77 mg/kg/hour for 48 hours (the highest dose tested in humans) was similar or lower than that obtained after a standard therapeutic single dose of ibuprofen (300 mg) (Reparixin Investigator's Brochure, 2014).

Due to extensive metabolism, unchanged reparixin was poorly or not excreted into the urine of rat, dogs and humans so that the PK profile of reparixin is not influenced by renal impairment (Reparixin Investigator's Brochure, 2014).

In vitro protein binding of [^{14}C]-reparixin showed that reparixin is highly bound (approximately 99%) to plasma proteins in rats, dogs, rabbits, cynomolgus monkeys and humans. Albumin is likely to be the major plasma binding protein in all species, accounting for 99.2% in humans (Reparixin Investigator's Brochure, 2014).

Reparixin has some potential in vitro for a non-competitive inhibition of the human hepatic enzyme CYP3A4 that is involved in the metabolism of cyclosporine A, tacrolimus and rapamycin. However, since inhibition is evident at concentration far higher than the free plasma concentration of reparixin at steady state (C_{ss}) in humans, it is predicted that the clinical relevance of such inhibition is remote. Indeed, reparixin does not affect to a clinically relevant extent the activity of CYP3A4 and CYP2C9 (enzyme involved in reparixin metabolism), as revealed by an interaction study where the PK of midazolam and tolbutamide (probe substrates for these enzymes) was evaluated in healthy subjects receiving single oral doses of the probes alone or in combination with reparixin (Reparixin Investigator's Brochure, 2014).

A 14-day oral toxicity and PK study has been performed in rats. It could be concluded from a comparison of the PK data, that the overall exposure to DF1681Y, in terms of overall exposure

(AUC_{tot}), attained in the i.v. continuous infusion studies, both in dogs and rats, was well above the AUC_{tot} attained in the 14 days oral study in the rats. At the same time, the maximum plasma concentration (C_{max}) attained was higher in the 14-day oral study in rats.

The PK profile of the oral formulation of reparixin has been studied in humans in a phase 1b clinical trial in metastatic breast cancer patients. In this study, reparixin was administered at 3 dose levels (400 mg, 800 mg and 1200 mg tid) as single agent for a 3 day run in period and then in combination with weekly paclitaxel for 21 days of each 28 day cycle. This trial has completed enrollment with 33 patients enrolled and data analysis is currently underway. Preliminary PK data from this study indicate that there is no pharmacokinetic interaction of Reparixin with Paclitaxel. Reparixin, in the oral tablet formulation, displayed a short half-life (mean $t_{1/2}$ <3 hrs) similar to the intravenous form. The increase in exposure with dose, following single dose administration and multiple dose administration was not linear in the dose range explored.

2.2.4 PRECLINICAL TOXICOLOGY PROFILE

Reparixin L-lysine salt was tested for toxicity in rodent and non-rodent animal species after single or repeated dose administrations. The repeated dose administration studies were conducted by infusional route and by oral route according to the human foreseen administration routes (Reparixin Investigator's Brochure, 2014).

The general toxicological profile of reparixin L-lysine salt, as for the studies conducted to date, is characterised by a low toxicity after single administration by i.v. or oral route to mice (LD_{50} = i.v. 609 mg/kg; LD_{50} = orally (p.o.) >3 g/kg) and to rats (LD_{50} = i.v. 348 mg/kg; LD_{50} = p.o. 1303 mg/kg) (Reparixin Investigator's Brochure, 2014).

Single ascending doses of reparixin L-lysine salt (DF1681B) and reparixin acid (DF1681Y) were administered orally (by gavage) to rats up to the dose of 1000 mg/kg twice daily (b.i.d.). The daily doses up to 2000 mg/kg were very well tolerated and no mortality, clinical signs or body weight changes were observed (Reparixin Investigator's Brochure, 2014).

The repeated dose administration to rats by continuous infusion for 28 days resulted in a determination of a safe dose of 1000 mg/kg/day (no observed adverse effect level [NOAEL]), while the continuous infusion administration to dogs for two weeks resulted in a safe dose of 60 mg/kg/day (in a preliminary study conducted in dogs at the dosage of 50 mg/kg/day/24 hours one male animal showed a mucosal ulceration in the fundic area of the stomach) (Reparixin Investigator's Brochure, 2014).

The repeated oral administration by gavage in rats for a period of 14 days up to the doses of 400 mg/kg b.i.d. resulted to be well tolerated and only minor adaptive liver changes of metabolic nature were observed in females at the dose of 400 mg/kg/b.i.d. They consisted of an increase in liver weight and hepatocellular hypertrophy. The no observed effect level (NOEL) could be determined at 400 mg/kg/b.i.d. in males. In females 400 mg/kg/b.i.d. represents the NOAEL (Reparixin Investigator's Brochure, 2014).

DF1681Y was administered twice daily (8 hrs apart) via gavage to SPF-bred Wistar rats at dose levels of 100, 200 or 400 mg/kg bw/bid for a period of 13 weeks. The treatment did not result in mortality, relevant clinical signs, body weight, food consumption, hematology, ophthalmoscopic examination or urinalyses. Minor changes in blood chemistry, organ weights and in the morphology of liver and of male kidneys at 400 mg/kg/bid were of no toxicological relevance and reversed after 4-week of recovery period. The NOAEL was settled at 400 mg/kg/bid (Reparixin Investigator's Brochure, 2014).

Continuous i.v. infusion of reparixin L-lysine salt to the male and female rat at dose levels of up to 1000 mg/kg/day did not have any significant adverse effects on mating performance and fertility (Reparixin Investigator's Brochure, 2014).

Reparixin poses no genotoxic hazard for humans (Reparixin Investigator's Brochure, 2014).

In order to provide evidence of the safety of DF2243Y, the main metabolite of reparixin excreted in urine in humans, safety pharmacology and toxicity studies have been performed at doses 2 to 3 times higher than those reached in man. Also, at this high level of exposure, no significant toxicity was observed (Reparixin Investigator's Brochure, 2014).

2.2.5 CLINICAL RESULTS

A total of 372 subjects have been involved in phase I and phase II completed clinical studies with reparixin. Among these, 236 subjects have been exposed to reparixin (Reparixin Investigator's Brochure, 2014).

2.2.5.1 Phase I Studies

Six Phase I PK/safety/pharmacodynamic studies have been conducted (Reparixin Investigator's Brochure, 2014).

In the first of these studies, reparixin L-lysine salt 1 to 16 mg/kg was administered by short infusion (30min). The compound was well tolerated at all doses, with minor and unspecific AEs which were not dose-related.

In the second study, the compound was administered as 48h i.v. infusion targeting to reparixin Css of 10, 20 and 30 µg/mL. Reparixin resulted well tolerated; again AEs were minor and not dose related. The local reactions were observed to subside by administering a more diluted solution at a higher infusion rate.

In the third study (interaction study), co-administration of midazolam/tolbutamide (probe substrates for CYP3A4 and CYP2C9) with reparixin did not raise safety concerns.

The fourth study was performed in subjects with different degree of renal impairment. The i.v. infusion of 2 mg/kg/h of reparixin L-lysine salt was safe and well tolerated both in patients with different degree of renal impairment and in subjects with normal renal function. Very few AEs were reported, the majority of which were mild in intensity and unlikely due to reparixin.

Two studies were performed in the cantharidin blister model to assess if reparixin can reduce the influx of PMNs inflammatory mediators, during acute inflammation. The safety of reparixin was confirmed in both of these studies.

2.2.5.2 Phase II Studies

Three Phase II studies have been completed to date (Reparixin Investigator's Brochure, 2014). Two studies investigating the efficacy of reparixin in the prevention of PGD/DGF in lung/kidney transplantation were conducted with reparixin administered by continuous intravenous infusion, up to a maximum of 48h. Neither of the two studies was able to show a statistically significant effect of reparixin on short- and long- term functional and clinical outcomes after transplantation. The AE profile was similar for both reparixin and placebo groups. SAEs were reported in 21 patients. SAEs possibly related to study drug were reported for only 2 patients, both in the reparixin continuous infusion group. An assessment performed by DMC on a possible study-related higher incidence of thrombosis, excluded the potential relationship of reparixin with these events.

A phase II study evaluating the efficacy of reparixin in improving transplant outcome in T1D patients undergoing pancreatic islet transplantation was conducted with reparixin administered by intravenous infusion over 7 days. Data obtained from this pilot trial further support the safety of reparixin in this clinical setting. The safety profile was in line with previous clinical experience and there were no safety issues that would preclude further development of reparixin in islet transplantation.

Due to encouraging data obtained in the pilot trial, a phase 3 study has been implemented and is ongoing in EU/ US to further evaluate the efficacy of reparixin in pancreatic islet transplantation. To date, 27 patients have been randomized, and 24 have gone on to treatment and transplant. 11 patients have received a second islet infusion.

In addition, a phase 2/3 is being conducted at 5 centers in the US to assess the efficacy and safety of reparixin in pancreatic islet auto-transplantation. To date, two sites are active and 5 patients have been randomized.

Two studies are ongoing in breast cancer patients. One is a phase 1b pilot study where reparixin oral tablets are given as single agent for a 3-day run in period and subsequently in combination with weekly paclitaxel in metastatic breast cancer patients to evaluate the safety, the PK profile and the effects of reparixin on Cancer Stem Cell (CSC) markers. This study began enrolment in February 2012 and has completed enrolment to all 3 dosing cohorts (400 mg t.i.d., 800 mg t.i.d., and 1200mg t.i.d.). An expansion cohort at the 1200mg t.i.d. dosing level was also initiated and completed enrolment in April 2014. The first data analysis is currently underway.

The second is a pilot "window of opportunity" clinical study in operable breast cancer patients where reparixin is administered as single agent in the time period between clinical diagnosis and surgery. This study aims to evaluate the effects of orally administered reparixin on CSCs in the primary tumor and the tumoral microenvironment in an early breast cancer population. Enrolment to this study began in April 2013 and continues in the enrolment phase.

2.2.5.3 Independent Studies

Two academic independent clinical trials have been conducted by the Medical University of Vienna (Reparixin Investigator's Brochure, 2014). In the first study the effects of reparixin on humoral and cellular parameters in lipopolysaccharide (LPS)-induced acute systemic inflammation was tested and in the second reparixin was studied in patients undergoing elective coronary artery bypass grafting with cardiopulmonary bypass (CPB).

2.2.6 SAFETY RESULTS

A total of 372 subjects have been involved in phase I and phase II completed (CSR issued) clinical studies. Among these, 236 have been exposed to reparixin (Reparixin Investigator's Brochure, 2014).

Phase 1 studies
A total of 136 subjects, of whom 103 adult healthy volunteers (including 3 females) and 17 patients with different grades of renal impairment (including 5 females) and 16 patients undergoing cardiopulmonary bypass (including 6 females), have been treated with reparixin.

Phase 2 studies
A total of 100 patients, 46 undergoing lung transplantation (23 male and 23 female), 48 patients undergoing kidney transplant (including 17 females) and 6 patients undergoing intrahepatic islet transplantation (3 male and 3 female) have been treated with reparixin.

Appendix 8 summarizes Cumulative Adverse Drug Reactions (ADRs) from completed studies with a CSR issued. It includes data from the studies mentioned above and from 14 healthy volunteers concomitantly treated with reparixin and the two probe drugs (midazolam/tolbutamide), therefore the ADRs evidenced in this group were included in this evaluation even though they were reasonably related to the pharmacological properties of the two probe drugs.

Exposure included short or prolonged i.v. infusion being 10.6 mg/kg over 30 min, 133.9 mg/kg over 48 h and 465.7 mg/kg over 7 days respectively the maximum administered doses of reparixin.
Reparixin was generally well tolerated at all doses studied. Overall, 115 ADRs were reported in a total of 70 subjects out of 236 exposed to reparixin (phase 1 studies: 71 ADRs in 45 subjects out of 136 treated; in Phase 2 studies: 44 ADRs in 25 subjects out of 100 treated).

The most frequent (>10%) ADRs observed in the phase 1 and phase 2 studies were:

Nervous system disorders (about 22%), including headache, dizziness, hypoaesthesia, somnolence.
Gastrointestinal disorders (about 22%), including nausea, vomiting, abdominal pain, dyspepsia, flatulence, gastroesophageal reflux disease.

General disorders and administration site conditions (about 19%), including cannula site reaction, injection site thrombosis, infusion site oedema and peripheral oedema, fatigue, lethargy.

The relatively high frequency of the administration site reaction is due to a cluster of events occurring in cohort 1 of the 48 h-infusion study. The use of a less concentrated solution with increased administration volume, i.e. increased infusion rate, in cohort 2 and 3 reduced the incidence of infusion site reactions.

The safety of reparixin seems to be confirmed also in patients with different grades of renal impairment. Out of 17 such patients only 3 experienced mild ADRs. There were no increases of the ADRs in the lung and kidney transplant studies. A similar incidence of ADRs was also seen after intermittent or continuous infusion during the kidney transplant study.

Data obtained in the pilot trial in islet transplantation, using the i.v. formulation, further support the safety profile of the proposed dose, even after a 7 days i.v. administration, repeated twice in a few patients. Most frequent ADRs were erythema, hypotension, nausea, vomiting; the great majority of these were mild to moderate in nature and none required discontinuation of the Investigational Product.

Both studies in breast cancer using reparixin oral tablets are ongoing. An update of safety information is outlined below:

In the phase Ib trial of combination paclitaxel and reparixin in metastatic breast cancer patients, all reported SAEs were considered unrelated or unlikely to be related by the treating investigator. No DLTs have been observed and the Safety Monitoring Committee approved escalation of the reparixin dose at each of the dose levels to reach the maximum studied dose of 1200 mg t.i.d. From preliminary data, the most frequent ADRs reported to date are dyspepsia, feeling of fullness, nausea, fatigue. All were mild to moderate in intensity and only in one patient discontinuation of IP was required. The ADR quickly resolved after study drug discontinuation. There may be a temporal relationship of gastrointestinal AEs to paclitaxel or the combination as the onset of gastrointestinal events often occurs in the days immediately following paclitaxel dosing. No gastrointestinal AEs were reported during the reparixin single agent run-in period, although this was a short run in consisting of 3 days treatment to perform PK evaluations. Grade 3-4 toxicities (according to CTCAE version 4.03) have been recorded in a minority of patients and about half consisted of haematological toxicities in patients receiving myelotoxic chemotherapy. G≥2 Peripheral neuropathy was not reported in any of the 33 patients, which is lower than expected in patients undergoing weekly treatment with paclitaxel and particularly for long periods of time. Peripheral neuropathy is the most common non-hematological toixicity of taxanes. With weekly paclitaxel, G3-4 peripheral neuropathy has been reported in about 15-20% of patients (Miller K et al., 2007), (Seidman A et al., 2008). In a preclinical study reparixin showed potential to reduce CXCL8-induced motor neuron degeneration in a rat model (De Paola et al., 2007). No neuroprotective agents are currently approved and the present trial represents an ideal setting to explore the potential of reparixin in prevention of taxane-induced peripheral neuropathy.

In the pilot window of opportunity trial for early stage breast cancer patients, only one unrelated SAE has been reported to date out of 18 patients enrolled. All AEs recorded thus far have been mild to moderate.

3 TRIAL RATIONALE AND OBJECTIVES

3.1 Rationale

The CSC concept has important implications for understanding carcinogenesis as well as for the development of novel cancer therapeutics.

In BC, CSC were originally identified as cells expressing the CD24-CD44+ phenotype (Al-Hajj, et al., 2003). Later, CSC in breast and also other human cancers were found to express the enzyme aldehyde dehydrogenase (ALDH+). ALDH+ as well as CD24-CD44+ cells can be identified either by assaying live cells with flow cytometry or by IHC in paraffin-embedded clinical specimens (Ginestier, et al., 2007). In breast carcinomas, the ALDH+ phenotype shows only partial overlap with the CD44+CD24–CSC phenotype (Ginestier, et al., 2007 & Liu, et al., 2013).

Numerous clinical studies have addressed the role of CSC in breast cancer. In patients undergoing neoadjuvant chemotherapy, it has been shown that the percentage of CSC increase following administration of chemotherapy even when the tumor shrinks, highlighting the chemoresistance of such cells (Li, et al., 2008 & Creighton, et al., 2009 & Tanei, et al., 2009).

A recent meta-analysis investigated the prognostic role of CSC in BC and found that presence of CSC is associated with a negative outcome. One prospective study in BC patients undergoing neoadjuvant chemotherapy came to the same conclusion (Alamgeer, et al., 2014). Overall, clinical data are in keeping with experimental findings and identify BC CSC as a novel therapeutic target.

One of the therapeutic strategies being pursued to target CSCs involves inhibition of self-renewal or survival pathways in these cells. These pathways include NOTCH, Hedgehog, and WNT (Korkaya, 2007). Such strategies may be limited by the role of these pathways in normal stem cell function, which could result in systemic toxicities from pathway inhibition.

In addition to intrinsic pathways regulating stem cell functions, normal and malignant stem cells are regulated by extrinsic signals generated in the microenvironment or CSC niche. In the breast, this niche is composed of immune cells, mesenchymal elements that include fibroblasts, endothelial cells, adipocytes, and extracellular matrix components (Brisken, et al., 2007). These components play an important role in normal breast development and carcinogenesis. If the cellular microenvironment plays an important role in the regulation of CSC growth and survival, then strategies aimed at interfering with these interactions represent a rational approach to target BC CSCs.

Gene expression profiling of the ALDEFLUOR+ populations of BC CSC revealed selective expression of CXCR1, a receptor for the cytokine CXCL8 (formerly IL-8). CXCR1 expression was limited to a proportion of ALDEFLUOR+ cells. *In vitro*, addition of recombinant CXCL8 increased the CSC population as well as its propensity for invasion (Charafe-Jauffret, et al., 2009). Furthermore, tissue damage induced by chemotherapeutic agents may induce CXCL8 secretion as part of the injury response (Ginestier, et al., 2010 & Bhola, et al., 2013). Using CXCR1-blocking antibodies or reparixin (a small molecular weight allosteric inhibitor of CXCR1), it was demonstrated that CXCR1 blockade selectively decreased the breast CSC population *in vitro* and in NOD/SCID xenograft models. Also the CD24-CD44+ BC CSC population was reduced following treatment with reparixin in the same NOD/SCID xenograft models (Ginestier, et al., 2010). It was shown that CXCR1 blockade induced massive apoptosis in bulk tumor cells via a bystander effect mediated by FASL/FAS signalling. CXCR1 effects on

CSC viability as well as FASL production were mediated by the focal adhesion kinase/AKT/forkhead transcription factor FKHRL1 (FAK/AKT/FOXO3A) pathway. Furthermore, administration of reparixin retarded tumor growth and reduced the development of systemic breast cancer metastasis in NOD/SCID mice (Ginestier, et al., 2010).

An independent report (Singh, et al., 2013) confirmed the role of CXCL8 in survival and proliferation of BC CSC. Overall, these data suggest that strategies aimed at interfering with the CXCL8/CXCR1 axis may be able to target CSCs, increasing the efficacy of current therapies which address the proliferating, non CSC component of the tumor.

However, reparixin or any CXCR1 inhibitor could hardly be applied as single agent to patients with metastatic BC, as eliminating the small population of BC CSC would do little in the short term to reduce tumor burden and preserve organ function, as observed also in tumor bearing animals (Ginestier, et al., 2010 & Bhola, et al., 2013).

Breast cancer can be divided in distinct subtypes based upon estrogen and progesterone receptor expression assessed by IHC and HER2 amplification evaluated by IHC and/or FISH. Triple negative breast cancer (TNBC) is characterized by both lack of expression of ER and PgR and lack of amplification of HER2 according to current guidelines (Hammond, et al., 2010 & Wolff, et al., 2013). TNBC represents roughly 15% of BC and currently is treated at diagnosis by surgery and (neo)adjuvant chemotherapy. However, a substantial proportion of patients relapse within 3 years from diagnosis and eventually succumb to the disease.

In metastatic TNBC, the general consensus on treatment with chemotherapy is a sequence of monotherapies in all cases, except those with a rapidly progressing or highly symptomatic disease (Cardoso, et al., 2012). TNBC biology on its own is not a sufficient reason to give combination chemotherapy (Cardoso, et al., 2012).

In TNBC, no prospective studies have established that the disease has particular sensitivity or resistance to any specific chemotherapy agent.

The taxanes, docetaxel and paclitaxel have been a mainstay in the treatment of MBC for many years. Currently, FDA approved dosing schedules in MBC of 175 mg/m^2 as a 3-hour intravenous infusion every three weeks for paclitaxel. However, paclitaxel administered as a weekly schedule (80-100 mg/m^2) has been studied extensively as a single agent in MBC as a means to increase dose density and improve tolerability. In a randomized Phase 3 trial weekly paclitaxel 80 mg/m^2 outperformed every three weeks paclitaxel 175 mg/m^2 in metastatic BC (Seidman, et.al., 2008). Several Phase 2 studies reported on the activity of single agent weekly paclitaxel in MBC (Eniu, et al., 2005). Response rates have been observed in the range of 22-53% in pretreated patients, with a median time to progression of 5-6 months. The toxicity associated with this regimen was mild and consisted mainly of neutropenia and peripheral neuropathy. Taxane-based regimens are the only standard of care in first-line therapy both in patients with TNBC diagnosed in stage IV and in patients with TNBC progressing after adjuvant anthracycline-based, non-taxane-containing chemotherapy regimens (Cardoso, et al., 2012). However, patients with TNBC who are newly diagnosed with metastatic disease or patients who do not receive (neo)adjuvant chemotherapy are rare given the aggressive behavior of this BC subtype (Awada, et al., 2014; (Isakoff, et al., 2011; Carey, et al., 2012; Baselga, et al., 2013; Smith, et al., 2011; Hamilton, et al., 2013; O'Shaughnessy, et al., 2011). TNBC patients commonly receive neoadjuvant treatment which often involves administration of a taxane. Taxanes have been proposed as a re-challenge regimen in patients with 6-12 months of disease-free survival following completion of neoadjuvant chemotherapy (Palmieri, et al., 2010). Re-challenge with a taxane as frontline treatment of metastatic disease has been specifically evaluated in one study. The taxane re-

challenge cohort study identified participants from 6 prospective neoadjuvant taxane-based studies with recurrent disease and collected data on their subsequent treatment. The response rate to taxane (either single agent paclitaxel or docetaxel) was dependent on the disease-free interval prior to re-challenge (<1 year 34.8%, 1-2 years 42.9%). 21 out of 35 patients re-challenged with paclitaxel responded (60%). The observed response rate for TNBC was 50% (Guo, et al., 2011).

TNBC is characterized by a CSC signature (Idowu, et al., 2012) which, coupled with sensitivity to chemotherapy, current lack of targeted therapies and dismal prognosis, makes this BC subtype an attractive candidate for a novel CSC targeting agent to be tested in combination with single agent chemotherapy. Moreover, the majority of the BC cell lines and patient-derived xenografts used in preclinical work with reparixin were TNBC (Ginestier, et al., 2010).

Reparixin oral tablets are being tested as a CSC targeting agent in patients with metastatic non-human epidermal growth factor receptor (HER2)-amplified BC. An open label Phase 1b clinical study (REP0111) is ongoing (enrolment completed) in five US sites, under IND # 112502, to test safety, tolerability, pharmacokinetics and detect early signs of antitumor activity of increasing doses of reparixin oral tablets in combination with a fixed dose of weekly paclitaxel. The study has demonstrated safety and tolerability of the combination across the three dose levels explored and recorded objective responses in the published range for single agent weekly paclitaxel in the target population (Eniu, et al., 2005). The highest dose level explored (i.e., 1200 mg t.i.d.) was identified as the recommended phase 2 dose. Durable responses have been recorded in patients with TNBC.

The current phase 2 study thus aims to evaluate the Progression Free Survival of patients with metastatic TNBC receiving reparixin in combination with paclitaxel versus paclitaxel alone.

3.1.1 Dose and Schedule Rationale

Reparixin administration in oncology is by the oral route and the toxicity studied by this route have been conducted to support clinical development in this indication, which complement the i.v. toxicity studies conducted in support of the transplantation studied.

Toxicology studies performed include a 28-day i.v study in the rat, one 14-day i.v study in the dog, and one each of a 14-day and 13 week oral study in the rat.

The repeated dose administration to rats by continuous infusion for 28 days resulted in a determination of a safe dose of 100 mg/kg/day (NOAEL); while the continuous infusion administration to dogs for two weeks resulted in a safe dose of 60 mg/kg/day.

The NOAEL, in the repeated (14 days) oral dose study in the rat is 400 mg/kg b.i.d. in females. The NOEAL from this study, converted to human equivalent dose (HED) is equal to 65 mg/kg b.i.d. and was used as a reference for the starting dose calculation in the phase Ib clinical trial.

The NOAEL was settled at 400 mg/kg/bid in the repeated (13 weeks) oral dose study in the rat.

The first clinical trial with oral reparixin was in metastatic breast cancer patients with the aim of establishing a safe and effective dose of reparixin in combination with weekly paclitaxel. No maximum tolerated dose (MTD) was established and the highest cohort dose of 1200 mg t.i.d. was well tolerated. A total of 20 patients have been treated at the 1200 mg t.i.d. dose in combination with paclitaxel at 80 mg/m^2 weekly 3 out of 4 weeks. No DLT's were observed and all SAE's were unrelated or unlikely related to reparixin. Several confirmed RECIST responses were observed, some of which were durable (> 6 months). Based on these results, we propose

the same dose and schedule of reparixin and paclitaxel for this current phase 2 study in metastatic triple negative breast cancer patients.

3.2 Objectives

The primary objective of the study is to evaluate Progression Free Survival (PFS), defined as the number of days between the date of randomization and the date of clinical disease progression (PD) according to RECIST criteria version 1.1, as assessed by Independent Radiology Review, or death for any cause, whichever occurs first, in patients with Triple-Negative metastatic breast cancer treated with the combination of paclitaxel and orally administered reparixin compared to paclitaxel alone.

The secondary objectives are:

- To determine Overall Survival (OS).
- To evaluate Objective Response Rates (ORR)
- To determine the median PFS (mPFS)
- To assess the safety of the combination of paclitaxel and orally administered reparixin.

The exploratory objectives are:

- To determine Median Time to new Metastasis (TTM)
- To determine the proportion of patients progressing with new metastatic lesions
- To compare the incidence and severity of peripheral neuropathy between the two treatment groups
- Evaluation of CSCs in metastatic tissue

4 STUDY PLAN

4.1 Study Design

This is a two arm, phase 2 study to evaluate the efficacy of the combination of paclitaxel and reparixin compared to paclitaxel and placebo in metastatic Triple-Negative breast cancer patients.

Centralized patient registration and randomization will be coordinated by the Contract Research Organization (CRO) (PRA Health Sciences) using IRT.

There will be 2 groups:

Group 1: paclitaxel 80 mg/m^2 i.v. (Days 1, 8, and 15 of 28-day cycle) + reparixin oral tablets 1200 mg t.i.d. continuing from D 1 to Day 21

Group 2: paclitaxel 80 mg/m^2 i.v. (Days 1, 8, and 15 of 28-day cycle) + placebo oral tablets 1200 mg t.i.d. continuing from D 1 to Day 21

Study drug (reparixin/placebo) will be administered orally every six to ten hours t.i.d. for 21 consecutive days during each cycle with seven days off treatment between each cycle. Paclitaxel

will be administered in combination with study drug (reparixin/placebo) as an i.v. infusion on Days 1, 8 and 15 of each 28-day cycle.

Combination treatment will continue until disease progression according to RECIST criteria version 1.1, withdrawal of consent or unacceptable toxicity, whichever occurs first.

Tumor response and/or progression assessments will be performed and documented every eight weeks according to RECIST criteria version 1.1.

Metastatic tissue samples will be analysed for evaluation of CD24-CD44+ and ALDH+ CSCs.

It is planned that approximately 60 centers located in the USA and Europe will participate in the study.

4.1.1 PATIENT PARTICIPATION

On Cycle 1, Day 1, paclitaxel will be administered at the clinic after the administration of study drug (reparixin/placebo). From that point forward, study drug (reparixin/placebo) will be self-administered t.i.d. (every 6-10 hours) for 21 days. Treatment (three weeks on and one week off) will continue until disease progression according to RECIST criteria version 1.1, withdrawal of consent or unacceptable toxicity, whichever occurs first. The next clinic visits are on Days 8 and 15 when a paclitaxel infusion is administered to the patient. The patients will return to the clinic again on Day 29/Day 1 of the next cycle. A diary card will be kept by the patient to record the self-administration of study drug (reparixin/placebo).

Blood samples will be taken from the patient throughout the study for hematology and clinical chemistry analysis.

Archival tissue samples or newly collected metastatic biopsy samples will be analyzed at the site's pathology lab to confirm diagnosis of TNBC. Metastatic tissue samples will also be analyzed centrally for the presence of CD24-CD44+ and ALDH+ CSCs.

4.2 Study Endpoints

The primary endpoint of the study is:

1) Progression Free Survival (PFS) defined as the number of days between the date of randomization and the date of clinical disease progression (PD) according to RECIST criteria version 1.1, as assessed by Independent Radiology Review, or death for any cause, whichever occurs first.,

The secondary endpoints of the study are:

1) Overall survival defined as the interval (days) between randomization and death from any cause
2) Objective response rates (ORR) defined as the percentage of the patients reaching complete remission (CR), partial remission (PR) or stable disease (SD) according to RECIST criteria version 1.1.
   Disease response (disease status up to progression of disease [PD]) at pre-study (baseline) and every eight weeks until the end of the study:
   - CR rate
   - PR rate
   - SD rate
   - PD rate
3) Median PFS (mPFS) where PFS is defined as the number of days between the date of randomization and the date of clinical disease progression (PD) according to RECIST criteria version 1.1, or death for any cause, whichever occurs first
4) safety of the combination treatment
   - Monitoring of AEs throughout the study and at the off-treatment visit
   - Vital signs will be assessed at Day 1 of each cycle and off-treatment visit
   - Physical examination will be assessed at pre-study, on Day 1 of each cycle starting from cycle 2 and at the off-treatment visit.
   - Concomitant medications will be reported at pre-study and at each visit throughout the study and at the off-treatment visit
   - Safety labs:
     - Hematology parameters (hemoglobin, white blood cell (WBC) and differential count, platelets) will be measured at pre-study and on Days 1, 8 and 15 of each cycle and at the off-treatment visit.
     - Clinical chemistry parameters (sodium, potassium, calcium, serum creatinine, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), urea, total bilirubin) will be measured at pre-study on Day 1 of each cycle and as clinically indicated, and at the off-treatment visit.

- Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocytes and urobilinogen parameters (by dipstick or in lab) will be measured at pre-study, throughout each cycle if clinically indicated and at the off-treatment visit.

Exploratory endpoints of this study are:

1) Median Time to new Metastasis (TTM), where TTM is defined as the interval (days) between randomization and the date of the first observation that the new lesion was detected at existing or new sites (Oxnard, et al., 2012)

   New lesions at existing or new sites will be assessed at each disease assessment timepoint

2) proportion of patients progressing with new metastatic lesions defined as the percentage of the patients who at progression display new lesions at existing or new sites

3) Peripheral neuropathy will be closely monitored throughout the study and at the off-treatment visit by the investigators to evaluate the extent of peripheral neuropathy.

4) Evaluation of CSCs in metastatic tissue

   Correlative studies: evaluate on paraffin-embedded metastatic tumor tissue:
   - CD24-CD44+ CSC (by IHC)
   - ALDH+ CSC (by IHC)

Full details of the study assessments are provided in Section 8 (Treatment Assessments).

4.3 Sample Size

The trial is designed to provide 80% statistical power to detect an improvement in PFS from 5 months with paclitaxel monotherapy in patients with metastatic TNBC (Awada, et al., 2014; Finn, et al., 2009, Harris, et al., 2006;Miller, et al., 2007) to 8 months with the addition of Reparixin, corresponding to a hazard ratio 0.625, when using a logrank statistic having (one-sided) 0.025 false positive error rate. This requires 142 PFS events and the approximate sample size will be 156 randomized patients (78 patients per group).
Due to extreme enrollment difficulties during the first 6 months of 2018, enrollment to the study was terminated early (30 July 2018) and the final sample size will be 123 randomized patients. No formal recalculation of sample size/required PFS events could be made under these circumstances and although the above assumptions remain, the true statistical power and hazard ratio will be known after database lock and will be presented in the CSR.

5 STUDY POPULATION

Patients with Metastatic Triple-Negative breast cancer, attending the breast cancer clinics at the sites, will be enrolled. Enrolment will be competitive. Sites will be allowed to enrol patients until the complete sample size is met.

5.1 Patient Selection Criteria

The patient selection criteria will be checked at the pre-study visit within 14 days before treatment with study drug (reparixin/placebo).

5.1.1 INCLUSION CRITERIA

1. Female aged ≥ 18 years.
2. Patients with pathologically documented metastatic triple negative breast cancer (TNBC), eligible for treatment with paclitaxel. **Paraffin-embedded tissue must be available from metastatic sites, if reasonably accessible, or from the primary tumor, to confirm the diagnosis of TNBC and for correlative studies (only on metastatic tissue).** Fifteen slides can be obtained if the full block is not available to be sent or released.

   TNBC will be defined as breast cancer with <1% ER+ and <1% PgR+ cells, and HER2 immunohistochemistry score of 0 or 1+ and/or in situ hybridization (ISH) with HER2 gene copy number <4 or a ratio of less than 2 between HER2 gene copy number and centromere of chromosome 17. Patients whose metastatic disease is TNBC are eligible even when their primary tumor expressed hormone receptors and/or HER2.
3. Patients must be newly diagnosed metastatic or must have relapsed following a prior (neo)adjuvant chemotherapy regimen. If a taxane (i.e., paclitaxel or docetaxel) was administered as part of the (neo)adjuvant regimen, PD must have occurred > 12 months from the end of previous (neo)adjuvant treatment. For non-taxane (neo)adjuvant regimen, PD must have occurred > 6 months from the end of previous (neo)adjuvant treatment
4. Patients with at least one baseline measurable lesion according to RECIST criteria version 1.1.
5. Zubrod (Eastern Co-operative Oncology Group [ECOG]) Performance Status (PS) of 0-1.
6. Life expectancy of at least three months.
7. Patients must be able to swallow and retain oral medication (intact tablet).
8. Able to undergo all screening assessments outlined in the protocol.
9. Adequate organ function (defined by the following parameters):
   a) Serum creatinine < 140 µmol/L (< 1.6 mg/dL) or creatinine clearance > 60 mL/min.
   b) Serum hemoglobin ≥ 9 g/dL; absolute neutrophil count ≥ 1.5 x 10^9/L; platelets ≥ 100 x 10^9/L.
   c) Serum bilirubin ≤ 1.5 x upper normal limit (UNL) except patients with Gilbert's syndrome
   d) Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≤ 2.5 x UNL but ≤ 5.0 x UNL in case of liver metastases; alkaline phosphatase (ALP) ≤ UNL but *i*) ≤ 2.5 x ULN in case of liver metastases and *ii*) ≤5 x ULN in case of bone metastases; albumin ≥ 2.5 g/dl.

10. No history or evidence by CT scan or MRI, of brain metastases or leptomeningeal disease.
11. No known hepatitis B virus (not due to immunization), hepatitis C virus, human immunodeficiency virus-I and -II positive status.
12. No history or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Medical Monitor, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion
13. Dated and signed IEC/IRB-approved informed consent.

5.1.2 EXCLUSION CRITERIA

1. Prior therapy for metastatic TNBC (chemotherapy, hormone therapy or biological therapy), Patients may receive bisphosphonates and other therapies to treat bone metastases, however if used, bone lesions will not be considered as measurable disease.
2. Less than four weeks since last radiotherapy (excluding palliative radiotherapy).
3. Pregnancy or lactation or unwillingness to use adequate method of birth control.
4. Neurological or psychiatric disorders which may influence understanding of study and informed consent procedures.
5. Active or uncontrolled infection.
6. Malabsorption syndrome, disease significantly affecting gastrointestinal function.
7. G>1 pre-existing peripheral neuropathy
8. Any other invasive malignancy from which the patient has been disease-free for less than 5 years with the exception of curatively treated basal or squamous cell skin cancer
9. Hypersensitivity to:
   a) paclitaxel
   b) ibuprofen or to more than one non-steroidal anti-inflammatory drug.
   c) more than one medication belonging to the class of sulfonamides, such as sulfamethazine, sulfamethoxazole, sulfasalazine, nimesulide or celecoxib; hypersensitivity to sulphanilamide antibiotics alone (e.g. sulfamethoxazole) does not qualify for exclusion.

5.2 Removing Patients from the Study

A patient should be withdrawn from the trial if, in the opinion of the Investigator, it is medically necessary or if it is the wish of the patient.

The study treatment will be discontinued at any time if any of the following events occur:

- Development of AE or unacceptable toxicity, precluding further therapy with the study drug.
- Documented disease progression.
- Severe protocol violations, such as an incorrect treatment administration, or a concomitant use of not permitted medications. Before removal, these cases should first be discussed with Dompé farmaceutici s.p.a.
- Patient request.
- Patient has been enrolled, but has not started study treatment (e.g. due to onset of AE, consent withdrawal etc before treatment could be started).

- Patient becomes pregnant.
- Treating physician decision in the patient's best interest.
- Request of Dompé farmaceutici s.p.a.
- Study end while a patient is still on treatment. The sponsor will allow any ongoing patients to continue treatment outside of the trial via post-trial access, following approval by local Ethics Committee and Competent Authorities according to local requirements

Any treatment discontinuation must be recorded on the case report form (CRF) by the Investigator, who will indicate date and reason(s) for treatment withdrawal. Unless the patient has withdrawn consent, the off-treatment visit assessments should be performed as detailed in Section 8.3.

Patients who come off study will not be replaced.

5.3 Discontinuation Criteria

The Investigator or Dompé farmaceutici s.p.a. may decide to terminate the study if in the opinion that continuing in the study poses unacceptable risks to the patients. If such a decision is reached, no further patients will receive study drug and the study will stop. The decision will be based on an overall assessment of safety and tolerability. The Data Monitoring Committee (Section 12.4) will review the data and decide if the study should be terminated.

In particular, the following should be closely monitored:

Liver function tests:

- Any considerable increase in AST or ALT or bilirubin values which, in the Investigator's opinion, are not compatible with underlying disease.

Renal function tests:

- Any considerable increase in serum creatinine values.

6 RANDOMIZATION

Before randomization, and any study related procedures, at study entry all patients must have given a written informed consent for the study. All patients who enter trial screening are documented in the Subject Screening and Enrollment Log (each new patient entered onto that center's log will have a progressive patient number which is used until the patient leaves the study). In order to request randomization to the study, all the pre-treatment evaluations must be completed (see Section 8.1) and a Subject Registration Form should be completed and submitted along with supporting documentation to PRA Health Sciences for review and approval. Following approval to randomize by the PRA Medical Monitor, investigators will randomize the patient through IRT by responding to the prompts within the system. Screen failed subjects may be re-screened up to twice at the Investigator's discretion (ie, total of 3 screens including initial screening). The subject will maintain the same subject ID number provided at the initial screening. Subjects must be re-consented if more than 30 days have elapsed between date of initial informed consent and date of re-screen/randomization.

Patients will be randomized in a 1:1 fashion between paclitaxel and reparixin vs paclitaxel and placebo using IRT. Randomization will be stratified between the two sub-populations, newly diagnosed metastatic patients and patients that have relapsed following a prior (neo)adjuvant chemotherapy regimen.
The randomization groups will be generated with a computer procedure by the method of random permuted blocks.

The randomization system will be prepared and implemented by the IRT vendor

Individual treatment codes will be provided via the IRT system to PRA Health Sciences and the Dompé Pharmacovigilance department for safety procedures.

The treatment codes will also be accessible to an Independent Statistician (liaison between the CRO database and DMC Biostatistician) who will generate the reports for the Data Monitoring Committee (DMC) evaluation (see Section 12.4).

7 STUDY TREATMENT

7.1 Investigational Medicinal Product (IMP): REPARIXIN or Placebo and non Investigational Medicinal Product (NIMP): PACLITAXEL

7.1.1 FORMULATION

The IMP (Reparixin and matching placebo) will be supplied to the study investigators by Dompé farmaceutici s.p.a. free of charge. The drug product is in the form of oral immediate release 600 mg tablets containing the active ingredient reparixin or placebo. Reparixin 600 mg immediate release or placebo tablets are white oblong tablets. Refer to Appendix 5 for Reparixin and Placebo Description and Composition.

The NIMP (Paclitaxel) is commercially available. The drug is presented as a clear, colourless to yellow, slightly viscous solution for infusion. Stocks of paclitaxel will be purchased directly from the supplier by the site pharmacy according to standard practice and will not be labeled for the study. Refer to Appendix 7 for paclitaxel package insert.

7.1.2 CONTAINER AND CLOSURE SYSTEM

Reparixin tablets and placebo tablets will be packaged in white PVDC/PE/PVC/Aluminum blister packages and should be stored at temperatures not higher than 30°C.

The drug is manufactured according to current Good Manufacturing Practice requirements.

Medication labels will comply with the Competent Authority requirements of each country involved and will be printed in a Multilanguage format. Refer to Appendix 6 for reparixin and placebo packaging and labeling details.

Dompé farmaceutici s.p.a. will supply all details and documentation regarding the study drug in the pharmacy manual. The investigator will also be provided with written procedures regarding ***the dispensing of the study drug to the patient***.

Paclitaxel will be obtained directly by the site from the manufacturer as a commercially available drug.

7.2 Dose and Route of Administration

Study drug will be administered with water prior to the start of the paclitaxel infusion on Cycle 1, Day 1 and then administered approximately every eight hours. It is preferable that reparixin is taken with food. However, if the patient is unable to eat, study drug may still be administered. When in combination with paclitaxel (Day 1, 8 and 15 of each cycle), reparixin or placebo will be administered every eight hours with about 250 mL water and a light meal or snack.

Group 1: paclitaxel 80 mg/m^2 i.v. (Days 1, 8, and 15 of 28-day cycle) + reparixin oral tablets 1200 mg t.i.d. continuing from D1 to Day 21

Group 2: paclitaxel 80 mg/m^2 i.v. (Days 1, 8, and 15 of 28-day cycle) + placebo oral tablets 1200 mg t.i.d. continuing from D1 to Day 21

Combination treatment will continue until disease progression, withdrawal of consent or unacceptable toxicity, whichever occurs first.

Study drug (Reparixin or Placebo) will be administered orally at the dose of 1200 mg three times daily (2 x 600 mg tablets every six to ten hours) for 21 consecutive days during each cycle with seven days off treatment between each cycle. If the patient forgets to take the study drug, it should be taken as soon as the patient remembers and the time of dosing should be registered in the patient diary.

Paclitaxel will be administered as an i.v. infusion on Days 1, 8 and 15 of each 28-day cycle. Premedication must be administered prior to each infusion. The choice of premedication drugs will be made according to each institution's standard procedure. During Cycle 1, a ± 1-day window will be allowed for study visits. After Cycle 1, a ± 2-day window will be allowed for study visits. For tumor assessment (i.e. scans) beginning at Week 8, a ± 3-day window will be allowed.

Prior to infusion, paclitaxel must be diluted using aseptic techniques in 0.9% sodium chloride injection, or 5% glucose injection, or 0.9 sodium chloride and 5% glucose injection or 5% glucose in Ringer's injection, to a final concentration of 0.3 mg/mL to 1.2 mg/mL. The diluted product should ideally be used immediately, or if not used immediately, storage times should not be longer than 24 hours at 2 to 8 ˚C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions. Diluted paclitaxel solutions should be administered through polyethylene-lined administration sets.

7.3 Drug Compliance

The Investigator should accurately complete all the Drug Accountability Forms. A patient diary will be provided in which patients will keep note of treatment administrations and any missed doses. Both will be checked by the monitor during site visits and be available for audit or inspection at any time.

7.4 Drug Storage and Accountability

Reparixin tablets and placebo tablets are packaged in white PVDC/PE//PVC/Aluminum blisters in the form of patient kits, numbered to maintain blinding and should be stored at temperature not higher than 30°C. The vials of paclitaxel must be stored per prescribing information (see Appendix 7).

The Investigator (or pharmacist in those countries where it is required that shipment is made directly to the hospital pharmacy) is responsible for receipt, proper storage and usage of study drug. Partially used or unused study drug boxes should be destroyed on site (and documentation of destruction provided to Dompé farmaceutici s.p.a.) or returned to Dompé farmaceutici s.p.a., at the end of the study. The Investigator, who will keep a cumulative inventory and dispensing records, will maintain all supplies under adequate security. Adequate record of receipt, use or loss of drug will be retained.

Patients will be given a diary card to record information about date, time and dose taken of study drug. At each scheduled visit before the start of a new cycle of treatment and at the off treatment visit, the diary should be reviewed with the patient for completeness.

7.5 Concomitant Therapies and Birth Control

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, including palliative radiation and bisphosphonates or other drugs for the palliative treatment of bone metastases, provided their use is documented in the patient records and on the appropriate CRF. The use of growth factors is allowed, according to local institution guidelines. The administration of any other anticancer agent is NOT permitted. Ibuprofen must not be administered in the pre-study period and concomitant to study drug treatment (including the 7 days off at each cycle) as it is a metabolite of reparixin. Inhibitors or inducers of CYP2C9 should not be administered in the pre-study period (starting from 28 days pre-therapy) and concomitant to study drug treatment (including the 7 days off at each cycle) as reparixin is metabolized by CYP2C9. See Appendix 9 for list of medications.

Similarly, the use of other investigational drugs is not allowed in the pre-treatment period (28 days prior to treatment) and treatment period of the study.

All concomitant therapies taken during the study from the first day to the end of treatment must be recorded in the specific section of the CRF.

Adequate methods of birth control must be adopted by subjects and their partners during the study treatment period and during the 6 months following the completion of study therapy. See Appendix 10 for list of acceptable methods of birth control.

7.6 Criteria for dose modifications and delays

For re-dosing with weekly paclitaxel, courses of paclitaxel should not be repeated until the neutrophil count is at least 1500 cells/mm^3 on Day 1 and 1000 cells/mm^3 on Days 8 and 15 and the platelet count is at least 100,000 cells/mm^3 (Days 1, 8 and 15) and in the absence of active infection. Patients who experience CTCAE Grade 4 thrombocytopenia (platelets <25,000/mm^3) or CTCAE Grade 3 peripheral neuropathy lasting < 7 days during paclitaxel therapy, should have dosage reduced by 20% for subsequent course. If a patient experiences G3 peripheral neuropathy lasting >7 days, paclitaxel dosing should be withheld until the adverse event returns to G≤2 and, when reinstated, paclitaxel dose should be reduced by 20% for subsequent courses. The incidence of neurotoxicity increases with dose.

In the event that elevated LFT's (greater than three times the baseline values of AST/ ALT and in addition, value >ULN, or greater than twice the baseline values ALP) are determined on a day that the patient is scheduled to receive treatment, the patient's study drug (reparixin/placebo) and

paclitaxel therapy will be held and the values repeated weekly. If LFT elevation is persistent > 14 days and not due to progressive disease, the patient should discontinue from study.

If values decrease within 14 days, the patient may be retreated at the same paclitaxel dose. If within 1 week the patient again has an increase in LFT's (greater than three times the baseline values of AST/ ALT and in addition, value >ULN, or greater than twice the baseline values ALP), the patient's study drug (reparixin/placebo) and paclitaxel therapy will be held and the values repeated weekly. The patient may subsequently continue on therapy at a paclitaxel dose reduced by 20% at the investigator's discretion. If dose delays of paclitaxel become necessary due to toxicity, study drug (reparixin/placebo) treatment will also be delayed until normal paclitaxel treatment resumes. Paclitaxel dosing can be delayed by a maximum of 2 weeks. This will be documented on the diary card and the CRF. Once treatment resumes after a dose delay, the patient will continue to take study drug (reparixin/placebo) tablets for a total of 21 days.

No dose reductions or dose delays of reparixin (independent of paclitaxel toxicity as described above) are foreseen. In the case of toxicity which may, in the investigator's judgement, be related to reparixin, guidance will be provided by medical monitor and sponsor on a case-by-case basis.

In case of IP discontinuation in the absence of disease progression, patients may continue receiving paclitaxel outside of the protocol, as this will be considered a new therapy, and will be followed up as patients without PD.

8 TREATMENT ASSESSMENTS

After obtaining written informed consent and checking whether all inclusion and exclusion criteria are met, patients will be included in the study. The visits comprise the implementation and documentation in the CRF of the following procedures:

8.1 Pre-treatment Evaluations

All pre-treatment evaluations are to be performed within 14 days ($\pm$ 1 day window) prior to the start of study treatment (see Study Flow Chart, Section 1.2), unless otherwise specified, and should be repeated within one week if abnormal.

Pre-treatment evaluations include:

- Assessment of demographic data and tumor characteristics
- Assessment of tumor history, surgery, radiotherapy and systemic therapies
- A complete medical history including a detailed history of primary diagnosis, prior treatment and baseline clinical conditions
- Confirmation of no current tumor therapy and check of current concomitant pharmacological or non-drug tumor treatments
- Complete physical examination including weight, height, BSA, pre-treatment signs and symptoms, and Zubrod PS (Appendix 2)
- An ECG
- Chest X-ray (if not already performed to follow tumor). A thoracic computed tomography (CT) scan may substitute the chest X-ray

- Laboratory tests:
  - Hematology: hemoglobin, WBC and differential count, platelets.
  - Clinical chemistry: sodium, potassium, calcium, serum creatinine, urea, total protein, albumin, AST, ALT, ALP, total bilirubin.
  - Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocytes and urobilinogen (by dipstick or in lab)
  - Urine or serum pregnancy test (women of childbearing potential only)

Routine laboratory tests performed within 14 days screening period even if before ICF signed are acceptable

Baseline disease status will be assessed and lesions will be defined as "target" (measurable lesions) or "non-target" (non-measurable lesions) according to RECIST criteria version 1.1. A minimum of one and a maximum of five (two per organ) lesions will be defined as target lesions. Pre-study disease evaluation should be obtained within 28 days of study treatment initiation. Copies of scans (CT, MRI of chest, abdomen, pelvis etc.) will be submitted to the central radiology vendor for review.

- A CT scan or MRI of the brain
- Specific monitoring of peripheral neuropathy
- Collection of tumor tissue, within 28 days of study treatment initiation, for confirmation of recurrent breast cancer
- confirmation of TNBC and correlative studies, including evaluation of CD24-CD44+CSC, ALDH+CSC.

8.2 On Study Evaluations

Patients will be randomized to the study through the IRT system.

The procedures to be performed and the time schedule ($\pm$ 1 day window at cycle 1 and $\pm$ 2 day window after cycle 1) are as follows (see Study Flow Chart, Section 1.2):

- Pulse rate, systolic and diastolic BP (after 3 mins in the sitting position) will be performed pre-study within 24 hours prior to the first study drug (reparixin/placebo) administration and then on Day 1 of subsequent cycles. From cycle 2 onwards, physical examination will be performed on Day 1 of each treatment cycle.
- At each visit any AE (including specific monitoring of peripheral neuropathy) experienced since the previous visit will be collected and graded according to CTCAE version 4.03 grading scale (Appendix 3).
- Concomitant pharmacological and non-pharmacological treatments will also be recorded throughout the study.
- Laboratory tests:
  - Hematology: hemoglobin, WBC and differential count, platelets, will be repeated weekly (Days 1, 8, and 15) during all cycles and more often in case of Grade $\geq$ 2 toxicity.
  - Clinical chemistry: sodium, potassium, calcium, serum creatinine, urea, total protein, albumin, AST, ALT, ALP, total bilirubin will be performed on Day 1 of each cycle and as clinically indicated.

- Urinalysis will be repeated during treatment only if clinically indicated.
- Urine or serum pregnancy test (women of childbearing potential only) prior to each treatment cycle.
- Assignment of new reparixin/placebo patient treatment kit through the IRT system on Day 1 of each cycle (if hematology and clinical chemistry results allow paclitaxel infusion).
- Reparixin/placebo and paclitaxel administration

– Disease response (disease status up to PD) assessed by the same method of assessment and the same technique as at pre-study for each lesion will be performed every eight weeks from the start of therapy until study end. A CT scan or MRI of the brain will be performed if patient presents with symptoms of brain metastases or PD of baseline lesions (it is not necessary for PD with new lesions). According to RECIST criteria version 1.1, CR or PR should be confirmed by further evaluations that should be performed no less than four weeks after the criteria for response are first met. Copies of scans will be submitted to the central radiology vendor for independent review.
– Review patient diary from previous cycle and dispense a new one at each scheduled visit prior to the start of a new cycle of treatment.

8.3 Evaluation at Off Treatment Visit (Termination or Withdrawal)

The off-treatment visit should be performed 14 to 28 days following the last dose of study drug.

At study termination or in the event of premature discontinuation, it must be ensured that the following evaluations have been performed:

– Complete physical examination, weight, Zubrod PS, pulse rate, systolic and diastolic BP (after 3 mins in the sitting position) and chest X-ray (or CT scan if performed at baseline)
– AEs (including specific monitoring of peripheral neuropathy) and concomitant pharmacological and non-pharmacological treatments
– Laboratory tests:
  - Hematology: hemoglobin, WBC count and differential count, platelets
  - Clinical chemistry: sodium, potassium, calcium, serum creatinine, urea, total protein, albumin, AST, ALT, ALP, total bilirubin
  - Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocytes and urobilinogen (by dipstick or in lab).
  - Urine or serum pregnancy test (women of childbearing potential only)
– Disease response assessed by the same method of assessment and the same technique as at pre-study for each lesion. The assessment should include a CT scan or MRI of the brain if patient presents with symptoms of brain metastases or PD of baseline lesions (it is not necessary for PD with new lesions). The disease assessments do not need to be repeated if done within four weeks prior to the off treatment visit or for patients off treatment without documented PD – such patients should continue with their established schedule of disease assessments (every 8 weeks from start of therapy). Copies of scans will be submitted to the central radiology vendor for independent review.

- Best overall tumor response (BOR) assessment: this assessment evaluation should be recorded in the CRF in the appropriate section of the last cycle of treatment received.
- Any treatment suspension or discontinuation during the study must be recorded on the CRF by the Investigator on the treatment administration page of the cycle of occurrence (in case of suspension) or on the Off Treatment page (in case of discontinuation). The Investigator will indicate date and reasons of treatment interruption and also duration in case of treatment suspension.
- Review patient diary

8.4 Follow-up Evaluations

After treatment discontinuation, any medical conditions (e.g., AEs, laboratory abnormalities) still present in the 30 days after treatment discontinuation or any new condition occurring in the 30 days after treatment discontinuation must be reported and followed until recovery or assessment of chronicity. The Investigator has to follow all events until they resolve or as instructed by the medical monitor. In particular, SAEs still present at the end of the study treatment period and for the subsequent 30 days must be followed until the final outcome is determined, even if this implies that follow up continues after the patient leaves the trial and, when appropriate, until the end of any planned follow up period foreseen by the study protocol.

Safety assessments can include performance status, physical examination, assessment of AEs and any other procedures (e.g., laboratory tests, chest X-ray) as clinically indicated.

Patients off treatment without documented PD should continue to have disease assessments every eight weeks until PD or another anti-cancer therapy is initiated, whichever comes first. Following PD, survival status will also be collected every 3 months until death or until 30 September 2019 (1 year after last enrolled subject off treatment) , whichever occurs first. This will allow further data to be collected for descriptive purposes, in addition to the data from unblinded ongoing subjects, as described in section 10.9

Any subjects still on therapy after 30 September 2019 will be allowed to continue their treatment, for as long as they receive clinical benefit, via post-trial access, only after approval by local Ethics Committee and Competent Authorities according to local requirements. Any such subjects will be followed for safety for as long as they are on treatment and their data will be reported to the local Ethics Committee as per local requirements. At the end of post-trial treatment, the investigator will be asked to provide to the Sponsor the reason for treatment termination and in the case of PD or death, the date on which this occurred.

8.5 Other Assessments

8.5.1 CORRELATIVE STUDIES

8.5.1.1 CSC Markers (CD24-CD44+, ALDH+ by Immunohistochemistry)

At pre-study an archival paraffin-embedded metastatic tumor sample or a newly collected biopsy from a metastatic site will be analyzed for the presence of CD24-CD44+ CSCs and ALDH+ CSCs.

Newly collected biopsies will be obtained at study sites, within 28 days of study treatment initiation, by a specialist and under radiologist supervision (where necessary). The tissue will be immediately placed into formalin after retrieval and the specimen will be embedded using paraffin at the study site prior to transportation to central laboratory for further processing. Cells will be stained with ALDH1 and CD24/CD44 specific antibodies and analyzed using immunohistochemistry.

9 EFFICACY ASSESSMENT

9.1 Efficacy Parameters

Tumor response is to be assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1, evaluating tumor response in target and non-target lesions, for patients with measurable disease (see details in Appendix 4 and Section 9.1.1).

Patients must have completed at least one course of treatment and performed at least one disease assessment to be considered evaluable for response.

9.1.1 EVALUATION BY RECIST VERSION 1.1

The response status of each patient with measurable disease at baseline will be assessed by the Investigator.

All treatment decisions related to tumor assessment will be based on the Investigator and local radiologist evaluation of scans

Measurable lesions (target):

Lesions that at baseline can be accurately measured in at least one dimension (longest diameter [LD] to be recorded) as ≥ 10 mm by CT scan, ≥ 10 mm by caliper measurement by clinical examination, or ≥ 20 mm by chest X-ray. A minimum of one and a maximum of five (two per organ) lesions will be defined as target lesions.

Non measurable lesions (non-target):

All other lesions, including small lesions (LD < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis) as well as truly non-measurable lesions.

All measurements should be recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as close as possible to the treatment start and never more than four weeks before the beginning of the treatment.

Lesions that are considered as truly non-measurable include the following:

- Leptomeningeal disease.
- Ascites.
- Pleural/pericardial effusion.
- Inflammatory breast disease.
- Lymphangitic involvement of skin or lung.
- Abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducing imaging techniques.

Note: *Tumor lesions that are situated in a previously irradiated area should not be considered measurable disease, unless these lesions are new lesions (i.e. lesions appeared after irradiation and before study treatment).*

If the measurable disease is restricted to a solitary lesion, its neoplastic nature ***NEED NOT*** *be confirmed by cytology/histology.*

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Overall evaluation of target lesions

Complete Response/Remission (CR)	disappearance of all target lesions.
Partial Response/Remission (PR)	at least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.
Progression of Disease (PD)	at least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD)	neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

Overall evaluation of non-target lesions

Complete Response/Remission (CR)	disappearance of all non-target lesions and normalization of tumor marker level.
Non-CR/Non-PD	persistence of one or more non-target lesion and/or the maintenance of tumor marker level above the normal limits.
Progression of Disease (PD)	appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

The **best overall response** is the best response recorded from the start of the treatment until disease progression/recurrence. The patient's best response assignment will depend on the achievement of both measurements and confirmation criteria (see also Section 9.1.2).

The overall responses for all possible combinations of tumor responses in target and non-target lesions, with or without the appearance of new lesions, are detailed below.

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

9.1.2 CONFIRMATION CRITERIA

The main goal of confirmation of tumor responses is to minimize the risk of overestimation of the response rate observed.

RECIST version 1.1 criteria:

1. PR or CR: changes in tumor measurements must be confirmed by further evaluations that should be performed no less than four weeks after the criteria for response are first met.
2. SD: measurements must have met the SD criteria at least once after study entry at a minimum interval between two measurements (eight weeks).

9.1.3 CENTRAL INDEPENDENT RADIOLOGY REVIEW

Copies of all scans will be submitted to the Central Radiology Vendor (Bioclinica Inc.) for independent review (see section 12.5). Each scan will be reviewed by two separate radiologists. In the case of disagreement of disease response, a third radiologist will act as adjudicator.

Further details are provided in the Independent Radiology Review charter.

10 SAFETY ASSESSMENT

The qualitative and quantitative toxicities will be evaluated.

10.1 Safety Parameters

All the following examinations will be included in the evaluation and analysis of safety.

10.1.1 VITAL SIGNS AND PHYSICAL EXAMINATION

Diastolic and systolic BP (after 3 mins in the sitting position) and pulse rate will be performed at pre-study within 24 hours of the first study drug (reparixin) treatment, on Day 1 of subsequent cycles and at off treatment visit. A complete physical examination will be performed at pre-study, on Day 1 of each cycle from cycle 2 onwards and at the off treatment visit. Any observed abnormalities relevant to each system and apparatus will be recorded.

10.1.2 CONCOMITANT TREATMENTS

Concomitant treatments (both pharmacological and non-pharmacological, including transfusions) will be reported at pre-study, throughout the study and at the off-treatment visit.

10.1.3 CHEST X-RAY

A chest X-ray (if not already performed to follow the tumor) will be performed at pre-study and at the off treatment visit. A thoracic CT scan may substitute the chest X-ray.

10.1.4 LABORATORY EXAMINATIONS

The following laboratory tests will be performed locally at the study sites as scheduled in Section 8:

- Hematology: hemoglobin, WBC and differential count, platelet count
- Clinical chemistry: sodium, potassium, calcium, serum creatinine, total protein, albumin, AST, ALT, ALP, urea, total bilirubin.
- Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocytes and urobilinogen parameters (by dipstick or in lab).

10.2 Adverse Events

The Adverse Event (AE) definitions and reporting procedures provided in this protocol comply with the current Code of Federal Regulations (CFR) 21 Part 312 and EU regulations.

Information about all AEs, whether volunteered by the patient, discovered by questioning or detected through physical examination, laboratory test or other means, will be collected and recorded on the AE page of the CRF, and followed as appropriate. An AE is any undesirable sign, symptom or medical condition occurring in a patient or clinical trial subject administered a medicinal product, even if the event is not considered to be treatment-related. AE monitoring should continue for at least 30 days following the last dose of study drug.

Any medical conditions/diseases, or cancer related signs/symptoms present in the 30 days before starting study treatment must be recorded on the Medical History/Baseline Conditions CRF, even if the patient already signed the Informed consent.
Medical conditions/diseases, or cancer related signs/symptoms present after starting study treatment are considered AEs only if they increase either in frequency or severity once treatment starts. **Diagnosis of Disease Progression per se (without any specific sign or symptom) occurring after starting study treatment will not be considered an AE/SAE. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE/SAE**. Death due to disease progression must be reported as an SAE, preferable specifying the cause of death, if available.

Abnormal laboratory values or test results occurring after the start of study treatment constitute AEs, only if they induce clinical signs and/or symptoms and require intervention/therapy, i.e. are clinically significant. In these cases, they will be recorded on the AE page of the CRF along with the signs, symptoms or diagnosis associated with them. In addition, each AE will also be described by:

- Its duration (start and stop dates).
- Severity grade using the CTCAE version 4.03 (Appendix 3).
- Its relationship to the study drug; (suspected/unsuspected).
- Action(s) taken.
- Outcome.

The severity of AEs and SAEs will be graded using the CTCAE version 4.03. Any AE not listed in the CTCAE will be graded as follows:

Grade Definition:

1. Mild
2. Moderate
3. Severe
4. Life-threatening or disabling
5. Death

10.3 Serious Adverse Events

Information about all SAEs will be collected and recorded on the SAE Form. To ensure patient safety each SAE must be reported to PRA Health Sciences Drug Safety within 24 hours of learning of its occurrence. A SAE is an undesirable sign, symptom or medical condition which:

1. is fatal;
2. is life threatening;
3. requires hospitalization or prolonged pre-existing hospitalization;
4. results in persistent or significant disability/incapacity;
5. constitutes a congenital anomaly or a birth defect;
6. is medically significant, may jeopardize the patient's prognosis, and may require medical or surgical intervention to prevent one of the outcomes listed above.

The events that required hospitalization for one of the reasons reported below are not considered to be SAEs:

- Hospitalizations planned before entry into the clinical study which is part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition.
- Hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Hospitalization for treatments, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen.

- Hospitalization for general care not associated with any deterioration in condition.
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of SAEs given above and not resulting in hospital admission.
- These events must be recorded in the AE page of the CRF where a variable will be ticked to indicate that they are not SAEs.

Any SAE occurring after the patient has started study treatment and during 30 days after the patient has taken the last dose of study treatment must be reported.

Serious adverse events occurring to a subject after the treatment of that subject has ended should be reported to the sponsor if the investigator becomes aware of them.

10.4 Adverse Event Collection

Information on all AEs (serious and non-serious, expected and unexpected, suspected and unsuspected) observed by the Investigator or reported by the patient, will be collected in the appropriate section of the CRF.

Information on all AEs will be collected as soon as study treatment starts and throughout the study until resolution of the event.

10.5 Relationship of AEs to the Investigational Product

The Investigator will assess the causality relationship between the AE and the investigational medication, according to the criteria in the Table below:

Relationship of the Adverse Event to the Investigational Product

None (Intercurrent Event)	An event that is not and cannot be related to the Investigational Product, e.g. patient is a passenger in a road traffic accident.
Unlikely (remote)	Relationship is not likely e.g. a clinical event including laboratory test abnormality with temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	Relationship may exist, but could have been produced by the patient's condition or treatment or other cause.

Probable	Relationship is likely, the AE abates upon discontinuation of Investigational Product and cannot be due to the patient's condition.
Highly Probable	Strong relationship, the event abates upon discontinuation of Investigational Product and, if applicable, re-appears upon repeat exposure.

Adverse events are to be considered unsuspected if the relationship to the study drug as described in the table above is none or unlikely, whereas a possible, probable or highly probable relationship would mean that the adverse event would be considered suspected.

An **Adverse Drug Reaction** (ADR) is defined as an adverse experience which is a reasonably likely to have been caused by the drug. Any AE reported in the study having a possible, probable or highly probable relationship to study drug will be considered as an ADR.

10.6 Reporting Procedures for Serious Adverse Events

Any AE meeting the definition of serious, occurring after the patient has started study treatment, during the study or during 30 days after the last dose administration must be recorded on the SAE Report form provided by PRA Health Sciences. Any SAE occurring to a subject after the treatment of that subject has ended should be reported to the sponsor if the investigator becomes aware of them

The SAE must be reported within 24 hours from the Investigator's knowledge of its occurrence to:

PRA Health Sciences Safety Faxline North America: 1-888-772-6919

PRA Health Sciences Safety Faxline Europe: +44 1792 525 720

PRA Health Sciences Safety Hotline North America: 1-800-772-2215

PRA Health Sciences Safety Hotline Europe: +49 621 8782 154

Email North America: CHOSafety@prahs.com

Email Europe: MHGSafety@prahs.com

The initial report should be completed with the information available at the time of reporting. PRA Health Sciences will check the data reported on the SAE form and forward relevant documentation by email to the Safety Manager, Dompé farmaceutici s.p.a. (Tel. +39 02 58383462; Fax: +39 02 36026913 e-mail: farmacovigilanza@dompe.com) within one **calendar day** during business days (reports received between close of business Friday and the start of

business Monday will be transmitted within one business day; in case of long weekends, source documents only will be forwarded within one calendar day).

Further information on the event and its outcome, if missing on the initial report as well as follow-up information, should be provided by the Investigator as soon as available and forwarded to PRA Health Sciences, following the same procedure and timelines as for the initial report. In case of death, a copy of the autopsy report, if performed, should also be provided.

Whenever more than one SAE is observed, the Investigator should identify which is the primary adverse event, i.e. the most relevant one. If other events are listed in the same report, the Investigator, along with their relatedness to the Investigational Product, should identify which adverse events are serious and which are non-serious. In any case, the Investigator is requested to record his/her opinion about the relatedness of the observed event(s) with the investigational medication.

10.7 Non Serious Adverse Events

No immediate reporting is required. The Investigator will document the event in source and fill in the AE Form contained in the CRF and will describe the complete AE evolution till its outcome.

Should a non-serious AE become serious, the Investigator will then follow the same reporting procedures as for SAEs.

10.8 Adverse Events Causing Treatment Discontinuation

If a patient is withdrawn from the study as a consequence of an AE, this must be recorded and reasoned in the CRF, and the patient must be followed up until the resolution of the AE or as instructed by the medical monitor.

10.9 Unblinding

In the case of an emergency, where knowledge of the individual patient's blinded treatment could influence further patient care, Investigators will be allowed to unblind study medication, directly through the IRT system and must notify the CRO's medical monitor so that the reason for any premature unblinding can be documented. Training is provided to investigators prior to authorization to use the IRT system and the unblinding function is outlined in the study specific user guide.

The randomization code will be broken when the last enrolled patient has completed her therapy, and once the database has been locked. Following database lock, the randomization code for each of the subjects enrolled will be communicated by letter to the PI at each site, who will then transmit the information to their subjects still on treatment or in active follow up. Any previously enrolled subjects, still on therapy after database lock may continue treatment unblinded until disease progression by RECIST version 1.1, withdrawal of consent, or unacceptable toxicity, whichever occurs first. The data from the unblinded ongoing subjects will be collected, for descriptive purposes. Ongoing subjects randomized to the placebo group will be able to discuss with their treating physician whether to discontinue placebo treatment and continue on paclitaxel alone. All procedures/tests and visit frequency will remain as described in protocol section 8.

10.10 Overdose

Cases of overdose (accidental or intentional) which result in serious adverse reactions are to be handled following emergency procedures, and reported within 24 hours from the Investigator's knowledge of its occurrence This includes reports related to drug intake with suicidal intentions and consequent drug overdose.

The administration of 3 or more additional tablets on any given treatment day will be reported as an overdose even if not associated with adverse reactions and shall be reported to PRA Health Sciences by e-mail or fax within 24 hours, in order to have information about symptoms, corrective treatment and outcome of overdose.

PRA Health Sciences Safety Faxline North America: 1-888-772-6919

PRA Health Sciences Safety Faxline Europe: +44 1792 525 720

PRA Health Sciences Safety Hotline North America: 1-800-772-2215

PRA Health Sciences Safety Hotline Europe: +49 621 8782 154

Email North America: CHOSafety@prahs.com

Email Europe: MHGSafety@prahs.com

The relevant documentation will be forwarded by PRA HS by email to the Safety Manager, Dompé farmaceutici s.p.a

10.11 Pregnancy

Female patients must inform the Investigator immediately if they become pregnant. The Investigator must inform PRA Health Sciences within 24 hours about the pregnancy, using the ''Pregnancy Reporting Form in Clinical Trials''. The relevant documentation will be forwarded by PRA Health Sciences by email to the Safety Manager, Dompé farmaceutici s.p.a

Any pregnancy leads to the immediate exclusion from the trial.

The procedure for the follow-up of any reported pregnancy is as follows:

From Onset of Pregnancy to Delivery or Termination:

- If onset of pregnancy is reported prior to the first administration of the trial medication or if the woman decides for planned abortion, the pregnancy will be followed until termination or delivery.
- Any reported pregnancy after the first administration of the trial medication has to be followed and documented by the Investigator until termination or delivery:

    - Initial report after information from the patient (the information in terms of a possible "high risk" pregnancy should be obtained from the trial patient and her gynecologist, respectively)
    - Follow-up report at the end of pregnancy (or at termination).

After Birth:

The birth of the infant has to be documented by the Investigator:

- Final report (the information in terms of "healthy child" should be obtained from the trial patient and her pediatrician, respectively).

Miscarriage, stillbirth and any malformation/disease must be reported as a SAE.

For documentation of any pregnancy outcome other than abortion, stillbirth or any malformation/disease the "Pregnancy Report Form" has to be used. The completed documents have to be provided by the Investigator within 24 hours after obtaining the information from the trial patient.

10.12 Reporting Procedure to IRB/IEC and to Regulatory Authorities

In addition to reporting the SAE to PRA Health Sciences, the Investigator must also comply with the requirements related to the reporting of SAEs to the IRB/IEC which approved the study. For reported deaths of a subject, the Investigator shall supply the sponsor and the Ethics Committee with any additional information requested.

The requirements of IEC/IRB differ from one state and indeed one country to another, however as a minimum requirement all serious unexpected ADRs, life-threatening problems or deaths must be reported to the IEC/IRB which approved the protocol as soon as possible and in no event later than:

(*a*) seven calendar days after becoming aware of the information if the event is fatal or life threatening; and

(*b*) fifteen calendar days after becoming aware of the information if the event is neither fatal nor life threatening.

In parallel, during the course of the clinical trial, Dompé (or designee) shall inform the Competent Authorities/FDA of any serious unexpected ADR. Reporting timeframe will be the same as described above.

Furthermore, Dompé shall follow up safety information and shall report final findings in a written safety report as soon as the relevant information is available.

If the results of an investigation show that an adverse drug reaction not initially determined to be reportable is reclassified as reportable, Dompé shall report such reaction in a written safety report as soon as possible, but in no event later than 7/15 calendar days after the determination is made.

Copies of all correspondence relating to reporting of any SAEs to the IEC/IRB should be maintained in the Investigator's Files.

Each IEC/IRB and Competent Authority/FDA and Investigator will be informed of all serious unexpected ADRs which are reported from other Investigators, as applicable according to law requirements.

10.13 Reporting of Paclitaxel adverse reactions and overdose

Paclitaxel is used both as combination therapy with Reparixin or placebo in the comparator arm and is defined as a non-investigational medicinal product (NIMP).

ADRs (serious or non serious) related to paclitaxel only (e.g. injection site reaction), will be notified by the Investigators to local Competent Authority per post marketing pharmacovigilance

law requirements, in line with CT3 Art 7.11.3. and applicable national law, notwithstanding the seriousness.

Unexpected Serious Adverse Events related to this NIMP will per definition not be SUSARs and need not be reported as SUSARs, but the investigator will report suspected Adverse Reactions to the NIMP to the MOHs or to the Marketing Authorization Holder (MAH) as per local requirements, as stated above..

SAEs related to both IMP and NIMP and SAEs originating from a possible interaction between the IMP and the NIMP will be processed as SUSAR, if unexpected.

Expectedness of events associated with paclitaxel will be determined according to the events listed for those drugs in the reference safety information for paclitaxel (Appendix 7).

Overdoses of paclitaxel leading to signs and symptoms shall be reported by the investigator as AE or SAE to the sponsor.

11 DIRECT ACCESS TO ORIGINAL DOCUMENTS

The Investigator/Institution must allow national and foreign Regulatory Authorities, individuals delegated by the Independent Ethics Committee (IEC)/Independent Review Board (IRB) or Dompé farmaceutici s.p.a. and their agents such as PRA Health Sciences to have free access to and to conduct the relevant verification of all the original documentation of the study, including the informed consent forms signed by the patients enrolled into the study, the relevant patient files and/or out-patient files. Those individuals who are given free access to the documentation must take every reasonable precaution to keep the identity of the patients and the proprietary information of Dompé farmaceutici s.p.a., as reserved information, in accordance with relevant applicable legislation.

12 CONTROL AND QUALITY ASSURANCE PROCEDURES

Monitoring of the present clinical trial is the responsibility of PRA Health Sciences.

Audit activities will be performed by PRA Health Sciences Quality Assurance (QA), under the supervision of Dompé QA except for audit to protocol/amendments, informed consent form and CRF that will be audited by Dompé QA.

According to GCP, a number of measures and procedures aimed to guarantee data quality and reliability are to be applied and followed in carrying out this clinical trial.

12.1 Clinical Monitoring and Identification of Source Data

The study will be monitored by regular monitoring visits in compliance with GCP and PRA Health Sciences Standard Operating Procedures (SOPs) to verify data entered and collected on the CRF(s). Monitoring will be performed by PRA Health Sciences**.**

The Investigator should agree to receive periodic monitoring visits, based on patients' enrolment rate or for other reasons, such as to verify SAEs.

At each visit, the Investigator or a designated member of the study personnel should be available to provide direct access to all study-related documentation, including the original patient notes, and to make any necessary corrections to the CRF and/or other study documents. Source documents should be available to support the data recorded in the CRF, apart from those data for which the CRF might be accepted as being the sole source document and that will be identified

on the source data identification list prior to study commencement . The confidentiality of the patients' identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

The monitor will provide the Investigator with all the study materials before the study starts and, during the course of the study, will check at least the following:

- Full compliance with ICH, GCP, the study protocol and applicable regulatory requirements.
- Patient recruitment.
- Patient compliance.
- Drug accountability.
- Signed Patient Informed Consent forms
- Completeness and accuracy of the CRF data and their consistency with the source documents (appropriate source data verification will be conducted on all CRFs).
- Verification of the facilities.
- Investigator's Trial Master File.

The monitor will ensure completeness of CRFs on an ongoing basis.

12.2 Audit

The Investigator/Institution must allow Dompé farmaceutici s.p.a. and its agents to conduct the audits as an integral part of the quality assurance system as well as inspections from the IEC/IRB and relevant regulatory authorities. The audit is an independent verification, separate from the monitoring activity, of the activities and of the documents to ensure that the activities pertinent to the study were duly carried out and that they were recorded, analyzed and transferred in compliance with the protocol, with GCP, with the relevant SOPs and with applicable legislation.

12.3 Inspections

The Investigator/Institution must allow national and foreign Regulatory Authorities to conduct inspections.

The Inspection on the part of one or more Regulatory Authorities consists of an official review of the documents, facilities, records and any other resource considered by the authorities to be connected with the study.

12.4 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established and will be responsible for safeguarding the interests of trial participants, and for enhancing the integrity and credibility of the trial. The DMC will assess the safety of the treatments during the trial, and will monitor the overall conduct of the clinical trial. The DMC will provide recommendations to Dompé about stopping or continuing the trial. To contribute to enhancing the integrity of the trial, the DMC may also formulate recommendations to Dompé relating to the selection/recruitment/retention of participants, their management, improving adherence to

protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DMC will operate independently of Dompé, and its members will not have connections to Dompé with the exception of the compensation to DMC members related to their activities.

The DMC will comprise three members. They will be a multidisciplinary group that will include:

- Two oncologists with extensive experience in clinical trial conduct
- A Biostatistician with substantial experience in the DMC process.

The DMC:

- Will review unblinded data. To this purpose, an Independent Statistician will liaise with the CRO statistician and will have access to those components of the database necessary to generate the reports to the DMC.
- Will be responsible for the ongoing (at least every 6 months) review of safety data throughout the trial. Primary among the safety data that will be reviewed are Serious AEs. In particular, the DMC will monitor liver (AST, ALT and bilirubin) and renal (creatinine) function tests.
- Will be advisory to Dompé and make recommendations to Dompé regarding the continuation of the trial and potential modifications to the design and conduct of the trial. These recommendations will be made in a manner to maintain confidentiality of emerging information about safety, unless access to certain data is needed to enable Dompé to make decisions about the DMC recommendations. Dompé will be responsible for promptly reviewing the DMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in the study conduct are required.

All details of the conduct and responsibilities of the DMC will comply with Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees and will be described in the 'DMC Charter' to be finalized during the set-up phase of the study and prior to the initiation of enrollment.

12.5 Independent Radiology Review

An independent radiology review (IRR) committee will be appointed to provide a blinded review of all images of participating patients. Copies of all scans will be submitted to the Central Radiology Vendor (Bioclinica Inc.) for independent review. Each scan will be reviewed by two separate radiologists. In the case of disagreement of disease response a third radiologist will act as adjudicator.

Progression and response will be evaluated according to RECIST 1.1 criteria. The primary endpoint will be PFS as measured from the time of randomization to the time of disease progression or death, whichever occurs first. The response obtained by the IRR will be considered the final response for study reporting purposes.

Further details are provided in the Independent radiology review charter.

13 DATA MANAGEMENT

The data management of this study will be performed by PRA Health Sciences. PRA Health Sciences will perform data processing according to approved procedures including database specifications, CRF tracking, central laboratory data reconciliation, SAE reconciliation, dictionary coding and data validation. A quality control of site responses to data queries will also be performed on this study. PRA Health Sciences will create a conversion program to produce CDISC SDTM datasets.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by written agreement between Dompé s.p.a's and PRA Health Sciences' project team.

Data will be transferred to Dompé farmaceutici s.p.a. by PRA Health Sciences.

Medical terms will be coded according to the following dictionaries:

- Medical Dictionary for Regulatory Activities (MedDRA) (latest available version) for AEs and Medical History;
- WHO-drug dictionary with the Anatomical the Therapeutic Classification code, for previous and concomitant drugs.

13.1 Case Report Form (CRF)

PRA Health Sciences will provide the electronic CRF customized for the study in compliance with the FDA 21 CFR part 11 and EU regulations.

For each patient enrolled in the study, a CRF will be completed as soon as the data concerning that patient are available. The data are the sole property of Dompé farmaceutici s.p.a. and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/regulatory Authorities, without written permission from Dompé farmaceutici s.p.a.

14 STATISTICAL CONSIDERATIONS

The statistical analysis will be carried out with SAS version 9.4 (or later versions) from the SAS Institute. All patient data collected on the CRF and on the Diary will be listed by patient, treatment group and center.

Appropriate descriptive statistics will be produced, according to the variable. For continuous variables, the data will be presented according to a clinically relevant discretization. For categorical data, frequencies and percentages will be presented. If appropriate, confidence intervals around the mean or the proportions will be presented.

The data will be presented in the Clinical Study Report. A Statistical Analysis Plan (SAP) will be issued describing details of all the statistical methods and analyses to be applied to trial results, including censoring methods for PFS and TTM and sensitivity analyses for PFS based on different censoring mechanisms. Censoring dates will be defined as the last date on which progression status was adequately assessed using either the date of the last assessment performed or the date of the clinic visit corresponding to these radiological assessments (FDA Guidance for industry. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics). Any deviations from the original statistical plan will be described in the Clinical Study Report.

All reasonable efforts will be made to prevent missing data. Methods for imputation of missing data will be presented in the SAP for the clinical trial. Censoring at the last adequate disease assessment will be applied to patients lost to follow-up. When intermediate visit(s) is/are missed, data from subsequent PFS/OS assessment will be included (FDA Guidance for industry. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics).

14.1 Efficacy Analysis

The Intent to Treat (ITT) population will consist of all patients who are randomized and will be based upon the treatment randomized, regardless of the treatment actually received. Patients will be in the ITT analysis whether or not they receive study drugs, because exclusions cannot be made for events occurring after randomization that could be influenced by the randomized assignment. The primary and secondary efficacy analyses will be presented primarily for the ITT Population.

For the primary endpoint, the PFS (as measured from the time of randomization to the time of disease progression or death, whichever occurs first) will be compared between treatment arms using stratified log-rank test. For secondary endpoints, OS will be compared between treatment groups using stratified log-rank test and Kaplan-Meier curves will be produced to estimate median PFS and median OS outcomes. Patients will be randomized to the two treatment groups with a 1:1 ratio.

In supportive analyses, Cox regression analyses may be performed if clinical factors potentially affecting PFS and/or OS will be identified.

The disease response by IRR (disease status up to PD) at pre-study (baseline) and every eight weeks until the end of the study based on RECIST version 1.1 criteria will be summarized by counts, percents and 95% confidence intervals and by treatment and stratification group.

14.2 Safety Analysis

Safety and tolerability analysis will be applied on the safety population (all patients randomized having taken at least one dose of the study treatment) and will be based on the treatment actually received.

AEs, physical examination, vital signs, concomitant medications and laboratory data will be considered for the safety analyses. Descriptive statistics will be provided for these variables.

AEs will be coded using the MedDRA dictionary at the Lowest Level Term. For each patient, AEs and all related information will be listed. Only treatment-emergent AEs (TEAEs) will be summarized. TEAEs are those which first occur or increase in severity or relationship to study drug after the first dose of study drug.

A summary of TEAE, including the number of events reported, the number and percentage of patients reporting at least one TEAE, the number and percentage of patients discontinuing due to a TEAE, the number and percentage of patients with at least one serious TEAE, and the number and percentage of deaths will be presented by treatment group and overall.

A breakdown of the number and percentage of patients reporting each TEAE, categorized by body system and preferred term coded according to the MedDRA dictionary, will be presented

by treatment group and overall. Counting will be by patient not event, and patients are only counted once within each body system or preferred term. A similar tabulation will be produced for those TEAEs related to study drug. In addition, a summary of events reported, categorized by severity will be provided by treatment group and overall. Patients with multiple events within a particular body system or preferred term will be counted under the category of their most severe event within that body system or preferred term.

A summary of TEAEs leading to discontinuation will be provided, grouped by body system and preferred term by treatment group and overall. A summary of SAEs will be provided by treatment group and overall, grouped by body system and preferred term. A listing of any patient with an AE and outcome of death will be provided.

Vital signs data will be summarized by descriptive statistics at schedule visit. Laboratory data will be summarized through descriptive statistics at scheduled visit and shift tables taking into account the change in the CTCAE version 4.03 grade from start to end of treatment. Hematological toxicity evaluations of thrombocytopenia, neutropenia and leukopenia and incidence of peripheral neuropathy will also be summarized by treatment group.

14.3 Exploratory Analyses

Median TTM will be evaluated by means of Kaplan Meier survival curves.
Proportion of patients progressing with new metastatic lesions will be evaluated using the Cochran-Mantel-Haenszel (CMH) test, stratified by the patient population (newly diagnosed vs relapsed).

The CSC markers (CD24-CD44+CSC and ALDH+CSC assessed by IHC) will be summarized by descriptive statistics (n, mean, standard deviation, median, minimum and maximum).

14.4 Assignment of Patient Number

Study sites will be identified on the basis of a specific site number. Each subject is uniquely identified in the study by a 6 digit patient number. After written informed consent has been obtained, patients will be assigned the patient number starting with a 3 digit site number followed by a 3 digit subject number in numerical ascending order by site (e.g. 001-001). This number will identify the patient during the whole screening and treatment period until the end of the study. Once assigned to a patient, the patient number will not be re-used. The patient number will be recorded in both the IRT (See section 6) and EDC.

15 ETHICAL ASPECTS

All the parties involved in the study agree and will verify that this study will be conducted in compliance with IRB/IEC, FDA and ICH GCP Guidelines – including Title 21 Part 56 of the USA CFR relating to IRBs and GCP as described in the United States FDA CFR (21 CFR § 50, 56, 312) and ICH E6 - in accordance with applicable ICH regulations regarding clinical safety data management (E2A, E2B(R3)), and with ICH regulations regarding scientific integrity (E4, E8, E9 and E10). In addition this study will adhere to all local regulatory requirements, requirements for data protection, and the declaration of Helsinki.

15.1 Independent Review Boards/Independent Ethics Committees

A clinical trial may be initiated only after receiving written approval by the IRB/IEC to which the Investigator Site makes reference to. Dompé farmaceutici s.p.a. must therefore receive the favorable opinion of the IRB/IEC of the facility where the clinical trial will be conducted before the Investigator may begin to screen or enroll any patients into the study. Dompé farmaceutici s.p.a. and the Investigator must submit all the necessary documents required for attainment of the approval to the IRB/IEC. A copy of the approval by the IRB/IEC must be available at Dompé farmaceutici s.p.a. facility before the initiation of the study at each site.

15.2 Information for the Patient and Informed Consent

Before the start of the study, the written information to be provided to the patients and the Informed Consent Form must be submitted for review and approval by the local IRB/IEC, together with the protocol.

The Informed Consent must be requested, obtained and documented by the Investigator in accordance with applicable legislation, with GCP and with the ethical principles which derive from the Declaration of Helsinki.

(For the details relevant to the procedure for requesting and obtaining the informed consent to be described in the protocol, see the ICH GCP E6, paragraphs: 4.3.3, 4.3.4, 4.8.2, 4.8.3, 4.8.4, 4.8.5, 4.8.6, 4.8.7, 4.8.8, 4.8.11, 8.3.2 and 8.3.11.

16 ADMINISTRATIVE PROCEDURES

16.1 Changes to the Study Protocol

Once the final clinical protocol has been issued and signed by the Investigator and the authorized signatures, it must not be informally altered. Clinical protocol amendments are alterations to a legal document (the clinical protocol) and have the same legal status and must pass through the appropriate steps before being implemented. In general, any important change which theoretically increases risk to the patients or a patient's study participation must be approved by the IRB/IEC prior to be effective. Minor changes and administrative changes need only notification to the IRB/IEC without approval.

Any subsequent amendments must be made on a separate sheet and must pass through the approval process. Dompé farmaceutici s.p.a. is responsible for ascertaining whether FDA/EU Competent Authorities must be notified of the clinical protocol change.

The Investigator and the Regulatory Department of Dompé farmaceutici s.p.a. will be responsible to notify, respectively, the IRB/IEC and FDA/EU Competent Authority, if major changes to the study protocol are agreed with a specific amendment, as foreseen by laws and/or regulations in force.

It should be noted that where an amendment to the protocol substantially alters the study design or the potential risks to the patients, a revised Informed Consent Form (ICF) will be reviewed and approved by the IRB/IEC and each participating patient will sign the revised ICF at their next study visit.

16.2 Suspension/Interruption of the Study

Should the trial be prematurely terminated or suspended for any reason, the FDA/EU Competent Authority and the IRB/IEC will be promptly informed in writing by the Investigator or by Dompé farmaceutici s.p.a., according to the Regulatory requirements and the procedures detailed in the GCP (ICH E6).

The Investigator will promptly inform the trial patients, assuring appropriate therapy and follow-up for all of them.

16.3 End of Study

One subject (510-001) is still on study treatment, following the final cut off for follow up on 30th September 2019. The subject will be allowed to continue her combination therapy, off protocol, via post-trial access, for as long as she continues to receive clinical benefit. The study will terminate as soon as post-trial access for this subject is approved by the concerned Ethics Committee and Competent Authorities, as per local requirements.

16.4 Archiving

The Investigator/Institution must ensure the archiving of the essential documents of the study as specified by GCP and in compliance with US FDA regulations (21 CFR 312.62[c]) and EU regulations. The Investigator/Institution must adopt all the necessary measures to avoid accidental or premature destruction.

The Investigator/Institution must store the specific essential documents for at least two years after the latest approval of an application for a marketing authorization and until there are no ongoing or foreseen applications for marketing authorizations, or until at least two years have passed from the formal interruption of the clinical development of the investigational medicinal product, and in any case, until Dompé farmaceutici s.p.a. has made a written notification that it is no longer necessary to maintain these documents. Nonetheless, these documents must be maintained for longer periods of time if so requested by relevant applicable legislation or by a specific agreement with Dompé farmaceutici s.p.a.

16.5 Use of the Information and Publication of the Results

The Investigator will have access to study data and recognizes that all the information provided by Dompé farmaceutici s.p.a., which has not been made available to the public, in regard to the investigational medicinal product (indication, patents, chemical formula, synthesis and formulation processes, study data or other information) is the property of Dompé farmaceutici s.p.a. and are strictly confidential. The Investigator may utilize this information exclusively for the conduct of the research, within the limits of the signed letter of agreement.

In regard to the data derived from this clinical research, the Investigator is obliged to provide all the results obtained to Dompé farmaceutici s.p.a. Dompé farmaceutici s.p.a. will support the publication of the data in due time in an appropriate peer-reviewed scientific journal.

Should the Investigator intend to divulge any of the results of the study, except for the notification of the AEs foreseen by current legislation in regard to Pharmacovigilance, he/she must communicate this intention beforehand to Dompé farmaceutici s.p.a. by means of a Registered Letter. Dompé farmaceutici s.p.a. must answer the request of the Investigator within 2 months of the date of receipt of the request.

Dompé farmaceutici s.p.a. will use the data derived from the clinical study in connection with the development of the drug and therefore may transmit this information, if necessary, to other Investigators and/or Regulatory Authorities.

16.6 Insurance Covering Public Liability

This study is covered by an insurance policy for the civil liability towards third parties, stipulated by Dompé farmaceutici s.p.a. with PRA Health Sciences, which is obliged to provide the amounts with the Client is required to pay, as being responsible by law, for reimbursement of capital, interest or expenses for any kind of damage caused by the pharmaceutical products, whether registered or not, which were administered during the course of clinical trials, in hospitals, private clinics and health professionals for clinical trials and experimentation, as well as for the damage caused following administration for pharmacological research and experiments with drugs and pharmacological formulations already registered in Italy and/or abroad, but with a different dosage from the one indicated by the Pharmaceutical Manufacturer, or with new drugs under evaluation, as well as for all the activities pertaining to or connected with the experimentation itself, such as, the technical administration of the drugs and the withdrawal of blood from patients participating in the study.

This insurance is valid also for:

- Responsibilities which may derive from the Investigators/Monitors, on the basis of experimentation conducted upon request of the Insured entity;
- Any responsibility for which the Insured entity is called upon to answer by law, regulation, internal requirements, standard procedures or methods.

16.7 Financing of the Study

The financial aspects of this study are described in detail in the contract between, or on behalf of Dompé farmaceutici s.p.a. and the Institution/s involved in this study. Financial Disclosure Statements will need to be completed, as requested by FDA CFR 21 part 54.

17 RESPONSIBILITIES OF THE INVESTIGATOR

The Investigator is aware of his/her responsibility towards Dompé farmaceutici s.p.a. for all the actions delegated by him/her to other members of his/her staff assigned to the conduct of the study. Except where specifically required, the wording "Investigator" used in this protocol and in the CRF, refers to the Investigator or the qualified person designated by him/her, who may carry out activities relevant to the clinical trial and sign the study documents on his/her behalf.

The Investigator is obliged to conduct the study in compliance with the study protocol and in adherence to GCP (ICH E6) and with the principles of the Declaration of Helsinki (1964) and subsequent revisions (Appendix 1) as well as in respect of applicable legislation.

18 FINAL STUDY REPORT

The Final Clinical Report will be written by PRA Health Sciences and then approved by Dompé farmaceutici s.p.a., and the Principal Investigator. It will be structured as an Integrated Clinical Report containing clinical comments based on the data generated by the Statistical Analyses. It will be written in compliance with the ICH E3 guideline for both content and format.

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20 APPENDICES

Appendix 1	**Declaration of Helsinki**
Appendix 2	**Performance Status Scale: Zubrod/ECOG**
Appendix 3	**Common Terminology Criteria for Adverse Events (CTCAE version 4.03)**

Appendix 1 - Declaration of Helsinki

The World Medical Association Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects--can be accessed via the following link:

http://www.wma.net/en/30publications/10policies/b3/

Appendix 2 - Performance Status Scale: Zubrod/ECOG

0 = Fully active; no performance restrictions

1 = Strenuous physical activity restricted; fully ambulatory and able to carry out light work

2 = Capable of all self-care but unable to carry out any work activities. Up and about >50 percent of waking hours

3 = Capable of only limited self-care; confined to bed or chair >50 percent of waking hours

4 = Completely disabled; cannot carry out any self-care; totally confined to bed or chair

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Appendix 3 - Common Terminology Criteria for Adverse Events (CTCAE) version 4.03

The CTCAE version 4.03 can be accessed via the following link:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Appendix 4 - Response Criteria (RECIST) Version 1.1

Response evaluation criteria using RECIST version 1.1. The full article can be accessed from the following link:

http://www.eortc.be/recist/

Appendix 5 - Reparixin and Placebo Description and Composition

Description and Composition of the Drug Product and placebo

The drug product consists of immediate release tablets for oral administration containing 600 mg of DF 1681Y (Reparixin).

The composition of the tablets is reported in the two tables below along with information on the function and quality standard of each ingredient.

Tablets are packaged in white PVDC/PE/PVC/Aluminum blisters and should be stored at temperature not higher than 30°C.

Composition of DF1681Y tablet

Names of ingredients	Formula %	Function of ingredient	Reference to quality standards
Reparixin (DF 1681Y)	66.67%	Drug substance	Internal monograph
Cellulose Microcrystalline	15.72	Diluent/ Disintegrant	Eur. Ph/USP.
Lactose monohydrate	10.53	Diluent	Eur. Ph./USP
Croscarmellose Sodium	4.0	Disintegrant	Eur. Ph./USP
Hydroxypropyl cellulose	2.23	Binder	Eur. Ph.
Colloidal silicon dioxide	0.35	Glidant	Eur. Ph./USP
Magnesium stearate	0.50	Lubricant	Eur. Ph.
Total	100%	-	-

Composition of placebo tablet

Names of ingredients	Formula %	Function of ingredient	Reference to quality standards
Reparixin (DF 1681Y)	---	Drug substance	Internal monograph
Cellulose Microcrystalline	47.42	Diluent/ Disintegrant	Eur. Ph./USP
Lactose monohydrate	43.27	Diluent	Eur. Ph./USP

Croscarmellose Sodium	4.0	Disintegrant	Eur. Ph./USP
Hydroxypropyl cellulose	4.46	Binder	Eur. Ph.
Colloidal silicon dioxide	0.35	Glidant	Eur. Ph./USP
Magnesium stearate	0.50	Lubricant	Eur. Ph.
Total	100%	-	-

Appendix 6 - Reparixin and placebo packaging and labeling details

Patient Kits will be identified with a PATIENT Kit No. which is allocated by the IRT system at study enrolment and every treatment cycle thereafter. Each kit consists of 1 box containing 9 blisters of 15 tablets each, for a total of 135 tablets (126 tablets for each treatment cycle, with 9 tablets overage). sufficient for one treatment cycle.

The labels will have a Multilanguage format. The template of the English label is provided below. Label content will be adjusted to meet local regulatory requirements.

NOTE: Patient Kit No. XXXXXX is allocated by the IRT system

A: PRIMARY PACKAGING

Specimen Label for each blister

Sponsor Dompé farmaceutici s.p.a. **STUDY REP0114 CRO: PRA Health Sciences** coded BATCH No.

PATIENT Kit No. XXXXXX

For clinical trial use only. Keep out of reach of children.
USA only Caution: New Drug-Limited by Federal law to investigational use.

B: SECONDARY PACKAGING

Specimen Label for each Patient Treatment Cycle Box [multilanguage booklet label]

STUDY REP0114 **Sponsor** Dompé farmaceutici s.p.a.; Via S. Lucia 6, Milano – Italy
Tel +39 02 58383.1
CRO PRA Health Sciences

PATIENT Kit No. XXXXXX
(contains one treatment cycle)

INVESTIGATIONAL PRODUCT: reparixin (600 mg) or placebo oral tablets

CONTAINS: 9 BLISTERS OF 15 TABLETS EACH; TOTAL 135 TABLETS

coded BATCH No. coded EXPIRY DATE mm/yyyy **DO NOT STORE AT >30°C**
DO NOT FREEZE

DIRECTIONS: Take the drug three times a day (2 tablets every 6-10 hours) for 21 consecutive days.
See additional instructions in the Diary Card.
Contact the Investigator should you have any questions.

For clinical trial use only. Keep out of reach of children.

USA only Caution: New Drug-Limited by Federal law to investigational use.

Appendix 7 - Paclitaxel Package Insert

Paclitaxel package insert can be accessed via the link below:

Taxol - FDA prescribing information, side effects and uses

Appendix 8 - Safety Details

Summary of Adverse Drug Reactions (ADRs) – I.V. Formulation

Number of Reports by Terms			Frequency
MedDRA Body System / LLT ADR term	**Non Serious**	**Serious**	
Blood and lymphatic system disorders	**3**	**2**	**4.30%**
Anaemia	2	**1**	
Coagulopathy		1	
Lymphadenopathy	1		
Cardiac Disorders	**1**	**0**	**0.9%**
Tachycardia	1		
Gastrointestinal Disorders	**22**	**3**	**21.7.%**
Abdominal pain NOS	1		
Dyarrhea	1		
Dyspepsia	1		
Flatulence	2		
Gastroesophageal reflux disease	1		
Gastrointestinal haemorrhage		1	
Nausea	11	1	
Vomiting	5	1	
General disorders and administration site conditions	**22**	**0**	**19.1%**
Cannula site reaction	13		
Fatigue	1		
Injection site thrombosis	3		
Infusion site oedema	2		
Lethargy	1		
Oedema	1		
Oedema peripheral	1		
Immune system disorders	**0**	**1**	**0.9%**
Lung transplant rejection		1	
Injury, poisoning and procedural complications	**1**	**1**	**1.7%**
Complications of transplanted kidney	1		
Drug Administration Error		1	
Investigations	**2**	**0**	**1.7%**
Blood amylase increased	1		
Liver function test abnormal	1		
Metabolic and nutrition disorders	**1**	**0**	**0.9%**
Hyperkalaemia	1		
Musculoskeletal and connective tissue disorders	**1**	**0**	**0.9%**
Arthralgia	1		
Nervous system disorders	**25**	**0**	**21.7%**
Dizziness	3		
Headache	8		
Hypoaesthesia	3		
Somnolence	11		
Psychiatric disorders	**4**	**0**	**3.5%**
Abnormal dream	1		
Restlessness	1		
Euphoric mood	2		
Renal and urinary disorders	**4**	**0**	**3.50%**
Renal failure	1		
Renal tubular necrosis	2		
Urinary retention	1		
Respiratory, thoracic and mediastinal disorders	**6**	**1**	**6.1%**
Bradypnoea	1		
Cough	2		
Nasopharyngitis	2		
Respiratory failure		1	
Sore throat	1		
Skin and subcutaneous system disorders	**9**	**0**	**7.8%**
Erythema	6		
Infusion site erythema	2		
Pruritis	1		
Vascular disorders	**3**	**3**	**5.2%**
Haemorrhage		1	
Hypotension	3		
Retroperitoneal heamorrhage		2	
TOTAL	**104**	**11**	
Table does not include ADRs reported from on-going studies			

Summary of Adverse Drug Reactions (ADRs) – Oral Formulation

Number of Reports by Terms						
N=207 events*	Non-serious ADRs				Serious ADRs	Total
MedDRA Body System/ADR Preferred Term	CTCAE Grade 1 n (%)	CTCAE Grade 2 n (%)	CTCAE Grade 3 n (%)	CTCAE Grade 4 n (%)	All CTCAE grades N (%)	
Blood and Lymphatic System Disorders	**2 (0.09%)**	**3 (1.4%)**	**3 (1.4%)**	**0 (0%)**	**0 (0%)**	**8 (3.8%)**
Anaemia	1	2	1	0	0	4
Neutrophil count decreased	0	1	2	0	0	3
Thrombocytopenia	1	0	0	0	0	1
Cardiac Disorders	**1 (0.5%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (0.5%)**
Palpitations	1	0	0	0	0	1
Eye Disorders	**0 (0%)**	**0 (0%)**	**1 (0.5%)**	**0 (0%)**	**0 (0%)**	**1 (0.5%)**
Ulcerative keratitis	0	0	1	0	0	1
General Disorders and Administration Site Conditions	**39 (18.8%)**	**13 (6.3%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**52 (25.1%)**
Chest discomfort	2	0	0	0	0	2
Fatigue	20	11	0	0	0	31
Asthenia	0	1	0	0	0	1
Feeling abnormal	1	0	0	0	0	1
Pain	1	0	0	0	0	1
Peripheral Oedema	11	1	0	0	0	12
Face oedema	3	0	0	0	0	3
Pyrexia	1	0	0	0	0	1
Gastrointestinal Disorders	**73 (35.3%)**	**9 (4.3%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**82 (39.6%)**
Abdominal distension	5	1	0	0	0	6
Abdominal discomfort	4	0	0	0	0	4
Abdominal pain	3	0	0	0	0	3
Constipation	5	3	0	0	0	8
Diarrhoea	2	0	0	0	0	2
Dry mouth	1	0	0	0	0	1
Dyspepsia	7	1	0	0	0	8
Dysphagia	1	0	0	0	0	1
Epigastric discomfort	1	0	0	0	0	1
Eructation	3	0	0	0	0	3
Flatulence	7	0	0	0	0	7
Gastroesopageal reflux disease	2	0	0	0	0	2
Gastrointestinal disorder	0	1	0	0	0	1
Headache	2	0	0	0	0	2
Lip pain	1	0	0	0	0	1
Nausea	16	2	0	0	0	18
Proctalgia	1	0	0	0	0	1
Stomatitis	1	1	0	0	0	2
Upper abdominal pain	1	0	0	0	0	1
Vomiting	10	0	0	0	0	10
Infections and Infestations	**0 (0%)**	**4 (1.9%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**4 (1.9%)**
Cellulitis	0	1	0	0	0	1
Herpes dermatitis	0	1	0	0	0	1
Upper Respiratory tract infection	0	1	0	0	0	1
Urinary tract infection	0	1	0	0	0	1
Injury, Poisoning, and Procedural Complications	**0 (0%)**	**1 (0.5%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (0.5%)**
Infusion related reaction	0	1	0	0	0	1
Investigations	**10 (4.8%)**	**1 (0.5%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**11 (5.3%)**
Alanine aminotransferase increased	2	1	0	0	0	3
Aspartate aminotransferase increased	2	0	0	0	0	2
Blood calcium decreased	1	0	0	0	0	1
Weight decreased	3	0	0	0	0	3
White blood cell count decreased	2	0	0	0	0	2
Metabolism	**7 (3.4%)**	**3 (1.4%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**10 (4.8%)**
Hypercalcaemia	1	0	0	0	0	1
Decreased appetite	6	3	0	0	0	9

Musculoskeletal	**3 (1.4%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**3 (1.4%)**
Arthralgia	1	0	0	0	0	1
Joint swelling	1	0	0	0	0	1
Pain	1	0	0	0	0	1
Nervous System Disorders	**12 (5.8%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**12 (5.8%)**
Dizziness	2	0	0	0	0	2
Dysgeusia	2	0	0	0	0	2
Headache	4	0	0	0	0	4
Peripheral motor neuropathy	1	0	0	0	0	1
Peripheral neuropathy	2	0	0	0	0	2
Sinus headache	1	0	0	0	0	1
Reproductive System and Breast Disorders	**1 (0.5%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (0.5%)**
Pelvic pain	1	0	0	0	0	1
Respiratory, Thoracic and Mediastinal disorders	**13 (6.3%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**13 (6.3%)**
Cough	4	0	0	0	0	4
Dysphonia	1	0	0	0	0	1
Dyspnoea	3	0	0	0	0	3
Epistaxis	2	0	0	0	0	2
Nasal congestion	1	0	0	0	0	1
Nasal dryness	1	0	0	0	0	1
Pneumonitis	1	0	0	0	0	1
Skin and Subcutaneous Tissue Disorders	**7 (3.4%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**7 (3.4%)**
Alopecia	2	0	0	0	0	2
Erythema	1	0	0	0	0	1
Palmar erythema	1	0	0	0	0	1
Rash	2	0	0		0	2
Skin hyperpigmentation	1	0	0	0	0	1
Surgical and medical	**1 (0.5%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (0.5%)**
Sinus operation	1	0	0	0	0	1
Total	**169 (82%)**	**34 (16%)**	**4 (2%)**	**0 (0%)**	**0 (0%)**	**207**

*ADRs continuing across more than one treatment cycle without complete resolution and reported more than once in CRF to reflect changes in CTCAE grade, will be reported in this table as single ADRs with worst CTCAE grade. ADRs occurring more than once per patient but not continuing (i.e. with clear break between one occurrence and the next) will be reported in this table as separate ADRs.

Safety details are updated annually in section 6.2 of Investigator's Brochure.

Appendix 9 – CYP2C9 Inducers and Inhibitors

The following medications should NOT be administered to study subjects during trial participation as reparixin is metabolized by CYP2C9.

CYP2C9 Inducers: rifampin, carbamezapine, aprepitant, bosentan, phenobarbital, St. John's Wort;

CYP2C9 Inhibitors: amiodarone, fluconazole, miconazole, oxandrolone, capecitabine, cotrimoxazole, etravirine, fluvastatin, fluvoxamine, metronidazole, sulfinpyrazone, tigecycline, voriconazole, zafirlukast

Appendix 10 – Acceptable methods of birth control

Birth control methods which may be considered as highly effective
Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control
methods.
Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable[1]
- intrauterine device (IUD)[1]
- intrauterine hormone-releasing system (IUS)[1]
- bilateral tubal occlusion[1]
- vasectomised partner [1,2]
- sexual abstinence [3]

1 Contraception methods that are considered to have low user dependency.
2 Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner
of the Women of childbearing potential (WOCBP) trial participant and that the vasectomised partner has received medical assessment of the surgical success.
3 sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse
during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the
preferred and usual lifestyle of the subject.

Acceptable birth control methods which may not be considered as highly effective

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide [4]
- cap, diaphragm or sponge with spermicide [4]

4 A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods